World Premier International Research Center Initiative (WPI)
FY2023 WPI Project Progress Report

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Research Center	Human Biology-Microbiome-Quantum Research Center (Bio2Q)		
Center Director	Kenya Honda	Administrative Director	Oltea Sampetrean and Haruhiko Siomi

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2024) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

- Prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

Summary of State of WPI Center Project Progress (write within **2 pages**)

Overview: This year was dedicated to establishing the center. We established the management system, internal regulations, and laboratory space. We have launched the new interdisciplinary graduate school program ("STaMP") and expanded our outreach activities. To accelerate joint research studies that fuse various disciplines in the center, we initiated and conducted biweekly scientific meetings where all members of the Bio-1, Bio-2, and Q cores participated. Consequently, team members of the Bio1, Bio2, and Q cores began to work together to tackle several scientific problems related to human biology and the microbiome and that were previously difficult to address. In particular, we focused on metabolites derived from the human gut microbiota. The vast majority of metabolites (>99%) have not been structurally and functionally annotated (thus remaining unidentified "dark matter"). To investigate the functions of metabolites produced by the microbiota in the interaction between microbes and the host, we started sharing clinical samples, bacterial culture collections, metabolomics techniques, organoid culture systems, neuroscience/connectomics, and computational technologies among members as follows.

Research of the Highest Global Level and Fused Disciplines: By leveraging samples from our centenarian cohort and through close and productive cooperation with our international collaborators, the microbiome team of the **Bio-1 core** uncovered a notably diverse range of phages within the gut microbiota of centenarians and identified genes with potential roles in the function of the intestinal barrier and resistance against infections. Two significant new insights into the interplay between the microbiome and dietary factors were obtained. First, a vitamin that is critical in enhancing the interaction between intestinal tuft cells and specific immune cell subsets, thereby maintaining intestinal health, was identified. Second, symbiotic microbes are responsible for synthesizing several D-amino acids in both humans and mice and they disrupt the stereo-dominance of L-amino acids. Studies by the metabolome team revealed atypical features of the glycerophospholipid metabolic pathway necessary for parasitic life cycle adaptation, identified microbially produced carbohydrates affecting insulin resistance, and identified two bioactive lipids with immunomodulatory effects. Shared resources have been enriched by the addition of a comprehensive dataset of non-targeted lipidomics across multiple mouse tissues at various life stages, and the spatial lipidomics platform currently under development will facilitate the visualization of the localization of bacteria-derived lipids in host tissues. Investigations by the genome dynamics team have provided a new conceptual framework for chromatin plasticity, namely

its regulation by transposable elements (TEs), thus presenting new avenues for the analysis of microbiome-guided epigenetic regulation of TEs. Our newly established genome-editing platform that efficiently manipulates autoimmunity risk alleles, as well as our joint studies with clinicians on autoimmune diseases, have advanced our insight into the functional relationship between genetic polymorphisms and human immunity. The human disease analysis team has organically increased the number of stool and plasma samples for all our ongoing studies, with a special emphasis on advancing microbiota assessments in Parkinson's disease.

The **Bio-2 core** expanded analysis platforms and modeling systems to elucidate homeodynamics in human organs. The imaging metabolomics team developed an AI-assisted automated system that facilitates the differential diagnosis of breast cancer through surface spectroscopy of needle biopsy samples and uncovered novel metabolic characteristics in cancers reported to contain intracellular pathogens. The organoid team successfully established lung and pancreatic cancer modeling and optimized functional models for human intestines and livers, as well as intestine-bacteria co-culture systems. The structural analysis team designed and started the setup of the laboratory environment and the research workflow of the new structural biology facility. To elucidate how microbiome-produced metabolites are sensed by enteroendocrine cells (EECs), the neuroregulation team developed a viral vector toolkit to specifically manipulate gene expression in subpopulations of EECs and vagal nerves. We shed light on mechanisms of synapse formation and maintenance related to hearing and conducted a longitudinal cohort study by gathering behavioral and neurophysiological data from infants with an elevated likelihood of autism spectrum disorder, thus opening new avenues for analyzing the relationship between microbiota and the nervous system. The humanized animal model team has successfully maintained germ-free marmosets until sexual maturity, culminating in the successful delivery of newborns, and has developed an automated 3D tracking system for the behavioral analysis of marmosets, which will be instrumental in uncovering brain-gut interactions in germ-free marmosets.

Q-core continued to explore the potential applications of both current and future quantum computing alongside artificial intelligence (AI) in the realm of human biology and the microbiome. We conducted trials for causal discovery using quantum computing, analyzed microbiome functions, and tested our algorithms optimized for quantum computers. Specifically, we used our algorithm, which applies a quantum kernel instead of a conventional Gaussian kernel, for causal discovery to enhance accuracy in low-data domains, and investigated its performance in various problem settings. We also quantified gene expression in the marmoset gut microbiome, uncovering overlooked bacterial genes and their environmental influences. Furthermore, we developed algorithms for black-box and large-scale data optimization using existing quantum computers. These results, along with the addition of two new members, allowed our Q core to start developing concrete collaborations with biology cores and designing the roadmap for the next ten years.

International Research Environment and Organizational Reforms: To further establish Bio2Q as a globally visible research center, Keio University approved the plan for a new research facility and began securing funds, including large donations. To increase the transparency, efficacy, digitalization, and globalization of the center's operations, Bio2Q implemented an industry-modeled, WPI-mission-centered project management system in English. We also provided the researchers with comprehensive support for their relocation, living requirements, and research in English. Operational reforms and support for foreign researchers can be readily expanded within Keio University, as needed.

* Describe clearly and concisely the progress being made by the WPI center project from the following viewpoints.

1. World-Leading Scientific Excellence and Recognition

1-1. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2023.
* Regarding the criteria used when evaluating the world level of the center, note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

Bio-1 Multidimensional Data Analysis Core

Microbiome Team (Honda, Atarashi, Tuganbaev, Sampetrean, Sasabe, Pan)

The human gut is home to a diverse array of intestinal bacteria, collectively known as the gut microbiota. These organisms are not merely incidental inhabitants, but play integral roles in critical aspects of human health, including digestion, immune responses, metabolic processes, and brain function. Our research focuses on the gut microbiota of centenarians who had lived for more than 100 years. Centenarians are particularly interesting because of their exceptional longevity and superior health status. We aimed to identify specific bacterial species that may contribute to healthy aging and their mechanism of action. The Atarashi group, in collaboration with Xavier at the Broad Institute in Boston performed metagenomic analysis of fecal samples from centenarians. This study revealed a notably diverse range of phages within the gut microbiota of centenarians, including an increase in genes associated with sulfide production (Johansen et al., 2023, App.1 – 20). Hydrogen sulfide production may play a role in enhancing the function of the intestinal barrier and boosting resistance against pathogenic infections.

In addition to exploring the microbial and phage components of the gut microbiota, we found that dietary vitamin B1 plays a critical role in enhancing the interaction between tuft cells and IL-4 producing group 2 innate lymphoid cells (ILC2s) and promoting a conducive environment for maintaining intestinal health (Cui et al., 2023, App.1 – 1). Understanding the complex interplay between the gut microbiota, dietary components, and host health opens new avenues for developing targeted interventions aimed at promoting longevity and enhancing the quality of life. The potential to manipulate gut microbiota through the introduction of beneficial strains, dietary modifications, or phage therapy offers promising strategies for disease prevention and health promotion.

The human gut microbiome constantly converts natural products from the host and diet to numerous bioactive metabolites. Dietary proteins are essential macronutrients that are digested to release free L-amino acids for absorption in the small intestine. Gut commensal bacteria modify various L-amino acids (e.g., L-alanine) into D-enantiomers, which become integral components of bacterial cell walls and modulate host immune responses (Sasabe et al., 2016; Suzuki et al., 2021). However, how the host manages diverse microbial D-amino acids and whether they affect host physiology or pathophysiology is largely unclear. In 2023, the group led by Sasabe revealed that symbiotic microbes commonly synthesize several D-amino acids in humans and mice and disrupt the stereo-dominance of L-amino acids in the host. During development, the host acquires the ability to eliminate microbial D-amino acids via catabolism and excretion in the kidneys (Gonda et al., 2023, App.1 – 54). Therefore, they provide fundamental insights into how the chiral balance of amino acids is governed in mammals and further expand the understanding of inter-domain molecular homeostasis in host-microbial symbiosis. Because microbial D-amino acids have a day-night rhythm in the host, we have now set out to elucidate the regulatory mechanisms of the host endocrine system by D-amino acids.

The gut microbiota also influences the central nervous system by modulating various physiological elements such as the immune response, intracerebral metabolites, neurotransmitters, endothelial cells, and blood-brain-barrier integrity. These factors, in turn, play crucial roles in the development of neoplasms of the central nervous system. Particularly, aggressive brain neoplasms tend to emerge and grow in conditions marked by a diminished immune response and altered metabolism, and often exploit the abundance of neurotransmitters, endothelial cells, and blood vessels. The group led by

Sampetrean focused on elucidating the role of microbiota-induced changes in brain tumor formation. Using an implantation model based on murine glioma stem cells, we found that tumor progression was significantly accelerated in germ-free mice. We subsequently examined autonomous changes in the tumor cell transcriptome, along with changes in the immune response and alterations in the cellular composition of the tumor microenvironment. Building upon these analyses, our current research encompasses the interrogation of tumor progression and microenvironmental changes in germ-free mice transplanted with human fecal samples. Subsequently, we intend to explore the possible impact of microbiota on the response of tumor cells to treatment with chemotherapeutic agents.

Metabolome Team (Arita, Soga)

Gut microbes have unique metabolic systems, and many of their complex metabolic networks and structural diversity, as well as their interactions with the food environment and host, remains unresolved. The diversity of lipid species and their modifications could potentially yield a wide variety of biological information as functional elements. The identification of new functional lipids often leads to a new understanding of the biology and pathophysiology of diseases. Advances in non-targeted lipidomic technology, developed by the Arita group revealed a considerably greater variety of lipid molecules in living organisms than previously thought. By combining non-targeted lipidomics, which facilitates comprehensive analysis of unknown metabolites, with MS/MS molecular spectral networking, which supports the structural estimation of unknown molecules, we aimed to elucidate the lipid diversity formed by the intestinal microbiota and the molecular mechanisms that regulate the complex metabolic network. In 2023, the Arita group conducted non-targeted lipidomics of *Entamoeba histolytica*, a protozoan parasite that causes amoebiasis, and revealed atypical features of the glycerophospholipid metabolic pathway necessary for parasitic life cycle adaptation, in collaboration with Mi-ichi at Nagasaki University (Mi-ichi et al., 2023, App.1 – 17). In collaboration with the Ohno group at RIKEN-IMS, we also conducted a metabolomic analysis of human fecal and plasma samples to profile the involvement of the microbiome in insulin resistance. A previous study has revealed that fecal monosaccharides are increased in individuals with insulin resistance and are associated with microbial carbohydrate metabolism (Takeuchi et al., 2023, App.1 – 16).

Although the impact of gut microbiota-derived hydrophilic metabolites such as short-chain fatty acids on immune cell function and development is well documented, the immunomodulatory effects of gut microbiota-derived lipids are still of interest. In 2023, we reported that lipid extracts from the feces of specific-pathogen-free (SPF), but not germ-free (GF) mice, exhibited regulatory T (Treg) cell-inducing activity. We conducted RP-HPLC-based fractionation and LC-MS/MS-based lipidomics to identify two bioactive lipids with Treg-inducing activity in vitro: 9,10-dihydroxy-12Z-octadecenoic acid (9,10-DiHOME) and all-trans retinoic acid (atRA), with Treg-inducing activity in vitro (Shiratori et al., 2023, App.1 – 73).

Understanding the molecular mechanisms underlying aging is crucial for enhancing healthy longevity. In 2023, we compiled a comprehensive dataset of non-targeted lipidomics across multiple tissues at various life stages in mice to explore the potential link between aging and lipid metabolism, considering sex (male/female) and microbiome (SPF/germ-free) dependencies. This study provides a valuable resource for illuminating potential links between bacterial lipid metabolism and host tissue homeostasis associated with aging (Tsugawa et al., in press).

The Arita group is engaged in developing spatial lipidomics platform by MALDI-mass spectrometry imaging (MALDI-MSI) to visualize the distribution and localization of various lipids in cells and tissues. Docosahexaenoic acid (DHA) and ultra-long-chain polyunsaturated fatty acids (ULC-PUFAs) are uniquely enriched in membrane phospholipids of retinal photoreceptors. In 2023, we applied the newly developed MALDI-MSI technology and revealed that long-chain acyl-CoA synthetase 6 (ACSL6) facilitates the local enrichment of di-DHA- and ULC-PUFA-containing phospholipids in the outer segment of the photoreceptor, thus supporting normal visual function and retinal homeostasis

in mice (Kuroha et al., 2023, App.1 – 15). This technology will contribute to elucidating host-microbiome interactions by visualizing the distribution and localization of bacteria-derived functional lipids in host tissues.

The Soga group has the world's largest platform for polar and charged metabolome analysis, with over 60 metabolomics instruments, and has collaborated with numerous researchers in various disciplines. Cancer cachexia, a complex metabolic disease that accounts for 20% of cancer-related deaths, was studied in collaboration with the Aichi Cancer Center to determine its metabolic background. Metabolomic analysis of multiple mouse models has revealed a decrease in the one-carbon (C1) metabolites of niacin, vitamin B6, and glycine-related subsets in the liver associated with cachexia. Integration of proteomics and metabolomics revealed a linear decrease in liver enzymes associated with B vitamin-dependent niacin, vitamin B6, and glycine-related C1 enzymes, along with their associated metabolites (Kojima et al., 2023, App.1 – 28).

Genome Dynamics Team (Siomi, Ishigaki, Solberg)

Human health is maintained through complex interactions between the microbiome and host genetics, which have for the most part not been comprehensively elucidated. The genome dynamics team investigated the biological mechanisms of transposable elements (Siomi Lab) and genetic polymorphisms (Ishigaki Lab) and their interactions with microbiomes.

The Siomi group worked on transposable elements (TEs), the major components of mammalian genomes. As the name implies, TEs jump or transpose within a genome, creating new insertion sites that in turn alter the sequences and structures of the genome. Therefore, these new insertion sites are either deleterious or neutral to the host, or may also be adaptive. We have been studying how the mechanisms by which TE activity regulates the host. We are currently focusing on the role of TEs in early embryonic development. The expression of certain TEs, including MERVL, is transiently upregulated at the two-cell stage in mouse embryos, coinciding with zygotic genome activation (ZGA) and acquisition of totipotency. We aimed to address the role of MERVL in embryonic development by employing various strategies to inhibit gene expression, including the knockdown and repression of transcription. This project was a major undertaking because knockout approaches were not feasible for MERVL, which is present in hundreds to thousands of copies of the genome. We developed an approach to effectively target gene expression to deplete and reduce the production of *MERVL* transcripts in the early stages of preimplantation embryos, and showed that nuclear expression of MERVL is required for accurate regulation of the host transcriptome and chromatin state during preimplantation development (Sakashita et al., 2023, App.1 – 11). These findings show that *MERVL* transcription governs host cell potency (i.e., differentiation potential, including totipotency and pluripotency), providing a new conceptual framework where chromatin plasticity is regulated by TE transcription (Guo et al., 2023, App.1 – 12). We are currently engaged in the identification and characterization of the transcription factors that activate MERVL in early embryos. Solberg was the primary person in the lab to carry out the project. Recent studies have shown that the maternal microbiome modulates fetal development and that microbiome stress signaling pathways activate TEs. Therefore, our studies on TEs are relevant to our understanding of microbiome-guided epigenetic regulation of TEs and basic microbiome-guided chromatin processes that modulate transcription.

The Ishigaki group has committed to elucidating the functions of genetic polymorphisms that affect human immunity. Therefore, we joined an international consortium to conduct large-scale genetic studies to identify risk polymorphisms and assess their immunological functions. We conducted a genetic association study on juvenile idiopathic arthritis and reported that its risk allele reduced TRAF1 expression and enhanced TNF production (Wang et al., 2023, App.1 – 61). We also conducted a genetic association study to test the allelic effect on gene expression using skin samples obtained from patients with psoriasis, and reported *LCE3C* as one of the candidate causal gene for psoriasis (Wang et al., 2023, App.1 – 61). In addition, we established an efficient genome editing

platform to artificially manipulate autoimmunity risk alleles in vitro and experimentally validate the molecular effects of a primary biliary cholangitis risk allele (Hitomi et al., 2024). We also collaborated with clinical researchers to examine the immune system phenotypic abnormalities of patients with autoimmune diseases and their transcriptome signatures, such as an increase in dendritic cell precursors in peripheral blood linked to rheumatoid arthritis treatment resistance (Yamada et al., 2023, App.1 – 65) and transcriptome signatures of age-associated helper T (ThA) cells that show clonal expansion and facilitate B cell antibody production in multiple autoimmune diseases (Goto et al., 2024). Furthermore, we have a track record of T-cell receptor repertoire analysis and recently extended our expertise in B-cell receptor (BCR) research. In collaboration with clinical researchers, we generated and analyzed the largest-scale BCR database of systemic lupus erythematosus (SLE) patients and found that BCR repertoire abnormalities in SLE are positively correlated with peripheral helper T cell transcriptomic signatures and negatively correlated with the number of somatic hypermutations in plasmablasts, suggesting the involvement of the extrafollicular pathway (Ota et al., 2023, App.1 – 63). These research activities contribute to elucidating the functional underpinnings of genetic polymorphisms and human immunity, which will form the basis for investigating host and microbiome interactions.

Human Disease Analysis Team (Seki, Yoshino)
The clinical picture of chronic diseases and conditions is extremely diverse, and a comprehensive analysis of large amounts of patient information is essential to comprehensively elucidate disease concepts. Below is a summary of the number of new samples acquired and the total for fiscal year 2023 for the ongoing main projects.
-Centenarian Cohort Study: Stool samples from 10 individuals (total: 224 individuals)
-Kawasaki Cohort Study (aged 85-90): Stool samples from 84 individuals (total: 350 individuals)
-Dementia Study: Plasma only from 431 individuals (total: 431 individuals), Stool & Plasma from 32 individuals (total: 36 individuals)
-Parkinson's Disease Study: Stool samples from 7 individuals (total: 64 individuals)

In particular, the incidence of Parkinson’s disease (PD) is rapidly increasing in our aging society, and the microbiome influences the pathogenesis of Parkinson’s disease and drug metabolism. Improving the medical care of patients with Parkinson’s disease necessitates the optimization of treatment and provision of tailor-made medications based on microbiota assessments. Seki is promoting the provision of optimal multidisciplinary team care for patients with PD at Keio University Hospital. Improving the medical care of patients with PD necessitates the optimization of treatment and provision of tailor-made medications based on microbiota assessments. Seki group constructed a multicenter database of more than 1,000 patients with PD. Moreover, they obtained clinical fecal samples from approximately 100 patients with PD at Keio University Hospital with informed consent and provided them to the Microbiome Team for further analysis.

Bio-2: Homeodynamics mechanistic analysis core
The Bio-2 core aims to establish an analytical platform and modeling system for elucidating the homeodynamics of human organs. In particular, we focused on how human organs establish a dynamic equilibrium in concert with a diverse range of gut microbes. To understand the interactions between multiple organs and gut microbes in humans, the Bio-2 core established organoid models (Sato team) and marmoset models (Sasaki team) to recapitulate intricate organ-microbe interactions. Because these interactions mediate metabolic, endocrine, immune, and neural networks, the Bio-2 core implements unique and advanced analytical systems encompassing imaging metabolomics (Suematsu and Hishiki teams) and neuroregulation (Yuzaki and Minagawa teams). Furthermore, to explore the interactions between microbe-derived metabolites and host tissues, we employed a structural-level analysis led by Aricescu and Suzuki teams.

Imaging Metabolomics Team (Suematsu, Hishiki)
In FY2023, we developed an AI-assisted automated system of surface-enhanced Raman spectroscopy (SERS) to differentially diagnose ductal carcinoma in situ (DICS) and invasive breast cancers in frozen needle-biopsied samples collected from patients with breast cancer (Kubo et al., 2023, App.1 – 25). We also discovered novel molecular mechanisms for the chemoresistance of triple-negative breast cancer (TNBC). PRMT1, a methylating enzyme that regulates three important glycolytic enzymes (PFKFB3, PKM2, and PHGDH), synergistically regulates these enzymes to preferentially deliver glucose to serine/glycine cleavage enzyme systems to accelerate protein arginine methylation and enhance de novo fatty acids and S-palmitoylation of the enzymes. To prove this in clinical biopsy specimens, we combined canonical molecular biology with advanced imaging mass spectrometry, which enabled us to demonstrate the distinct features of the distribution of metabolites between cancer cell nests and the surrounding cancer stroma. Our team also launched a project of bioimaging multiple metabolites in brain of common marmosets and mice engrafted with human-derived cancer cells using MR spectroscopy with the world largest scales of magnetic fields and bores (11.7T and 22-cm bore), that allowed us to monitor many different metabolites in regions of interests of the target organs or tissues without euthanasia.

Organoid team (Sato)
Recent developments in organoid technology have provided remarkable insights into the understanding of human organ development and transformation of normal tissues into cancers (Fujii et al., 2024, App.1 – 68). Indeed, we have recently established lung (Ebisudani et al., 2023, App.1 – 71; Fukushima et al., in revision; Shinozaki et al., in revision) and pancreatic (Tamagawa et al., in revision) cancer modeling. Although current organoid technology recapitulates various phenotypes of human organs, such as proliferation, differentiation, and stem cell self-renewal, observing sophisticated organ functions. Furthermore, the modeling of human multi-organ interactions is yet to be established. In FY2023, we focused on developing functional models of the human intestine and liver. By combining a newly developed trans-well culture platform and a flow-based mechanical force system, we successfully optimized the cell-matrix interface to promote intestinal villous structure formation (Sugimoto et al., 2021; Hanyu et al., unpublished). Using this platform, we further optimized the culture conditions to enhance intestinal differentiation based on the expression of absorption-related genes such as SGLT1. Despite this improvement, the absorptive function of the human intestinal epithelium remains below the physiological absorption levels. We recently noted that organoids lose their functionality over long-term culture. Therefore, we aimed to identify the factors that impair absorption during organoid culture and establish new culture conditions for more robust and reproducible functional modeling of intestinal absorption. We also developed a human colon organoid culture system with a mucin layer. This protocol allowed us to co-culture gut microbes for a week, which is a considerably more optimized outcome than that of our previous methods (Sasaki et al., 2020). We plan to further optimize this intestine-bacterial co-culture system for the WPI-Bio2Q research project.

Human adult hepatocytes are prone to transdifferentiation into cholangiocytes, which poses a significant hurdle in the functional modeling of human hepatocytes. In FY2023, we established a stable propagation and differentiation organoid culture system for adult human hepatocytes. Human hepatocyte organoids preserve various hepatocyte functions, such as gluconeogenesis, the urea cycle, drug metabolism, and bile acid synthesis (Igarashi et al., in revision). Interestingly, the regulation of bile acid synthesis by intestinal hormones is recapitulated in the organoid culture system, providing insights into multi-organ interactions, in this case, the gut-liver axis.

Structural Analysis Team (Aricescu, Suzuki)
To establish a new structural biology facility at Keio University, the Structural Analysis team worked on the setup of the laboratory environment and research workflow. The detailed configurations of

the equipment for cryoelectron microscopy (TFS Arctis for FIB-SEM, TFS KriosG4 for TEM), a high-pressure freezer (Wohlwend compact 03), and the protein production/purification system were discussed and determined. Most will be ordered in FY2023, and the remainder will be ordered in FY2024. The laboratory design for the new EM facility was carefully conducted, and its construction is ongoing. The plan was to complete it by June 2024, and to open the lab in summer; however, the repeated review of the lab layout to create a more optimized and safer EM facility in the limited space has led to a three-month delay. To minimize the delay, a part of the lab space for Arctis will be available for use by the end of August, and its installation will begin before construction of the entire lab is completed.

The team works at the MRC-LMB UK to develop a workflow for *in situ* structural biology, which will be implemented at Keio University. The team designed a new custom planchette for the successful freezing of tissue samples using a high-pressure freezer, had intensive training on state-of-the-art cryo-ET equipment (Hydra, Aquilos2, Scios, KriosG4 with Selectris X), and developed data collection/processing pipelines using multiple software packages (Serial EM, Tomo5, WARP/M, IMOD, Amira, AreTomo, TomoTwin, Relion, Scipion, etc.). As an example of successful *in situ* structural analysis, the ribosome structure at 6A local resolution was obtained by subtomogram averaging from mouse liver tissue and is being improved.

Neuroregulation Team (Yuzaki, Minagawa)

The nervous system, along with the immune, endocrine, and metabolic systems, plays a central role in regulating homeostasis in many organs of the body. The nervous system functions by forming a complex network of synaptic connections between neurons, and between neurons and their target organs. The Neuroregulation team focuses on the relationship between various peripheral organs and the nervous system. In FY2023, the team elucidated mechanisms of synapse formation and maintenance in the organ of Corti, which controls hearing (Saegusa et al., 2023, App.1 – 58). Since age-related hearing loss is caused by synaptic abnormalities, and hearing loss is the greatest risk factor for dementia, it is hoped that targeting synapses will lead to new therapies. Progress has also been made in understanding the molecules that regulate the formation and maintenance of neural circuits that mediate chronic itch associated with atopic dermatitis and contact dermatitis. On the other hand, how metabolites produced by the microbiome, nutrients, and bile acids are sensed by the nervous system is not well understood. The team is focusing on signals from enteroendocrine cells (EECs), which are scattered throughout the intestinal epithelium. EEC signals are transmitted via the sensory vagal nerve to the nucleus tractus solitarii in the medulla oblongata, and further integrated with various types of information in higher brain centers to control visceral, cognitive, and emotional functions relevant to certain psychiatric and neurological disorders. To comprehensively understand the relationship between the microbiome and the nervous system, the team aims to elucidate 1) how metabolites produced by the microbiome are sensed by EECs, 2) how EECs communicate with sensory vagal nerves, and 3) how signals are integrated in higher-order centers. To achieve these goals, Yuzaki et al. developed a viral vector toolkit to specifically manipulate gene expression in different subpopulations of EECs and vagal nerves. To elucidate the molecular mechanisms by which the EEC-vagal nerve contact site is organized, the group applied the X10 Expansion microscopy (X10 ExM) technique developed by Nozawa et al. (2022).

The Minagawa group explored the link between the gut microbiome and neurodevelopmental disorders, particularly autism spectrum disorder (ASD), by focusing on social cognitive abilities related to human interactions and attachment. To achieve this goal, they conducted a longitudinal cohort study spanning four years from birth, gathering behavioral and neurophysiological data from both typically developing infants (TL) and those with an elevated likelihood of ASD (EL). One notable finding of this study was the discovery of brain synchrony between mothers and three-month-old infants during breastfeeding. Synchronous activity involving the reward network, including the orbitofrontal cortex, was consistent across both TL and EL mother-infant dyads, providing the first

evidence of brain coupling in very young infants within these groups (Minagawa et al., 2023, App.1 – 6). Furthermore, in FY2023, the group developed an innovative AI-based method to extract social signals such as mutual gaze from video data, allowing for correlation with neural synchronous activity between two brains during real-world human interactions (Xu et al., 2023, App.1 – 19). This advancement opens up avenues for measuring mother-child interactions among TL and EL infants in future research.

Humanized Animal Model Team (Sasaki)

The common marmoset is an attractive non-human primate (NHP) model for research on neurological diseases because of the similarity of its brain structure and function to that of humans, along with its ease of breeding and handling. The team generated *Presenilin 1* mutant marmosets using gene editing to develop models of Alzheimer's disease (AD) and germ-free marmosets. Using these unprecedented NHP models, experimental systems were developed to explore the unknown mechanisms of AD pathogenesis and its interactions with microbiota.

This year, the team developed an automated 3D tracking system called The Full Monitoring and Animal Identification (FulMAI) system, for the behavioral analysis of marmosets (Yurimoto et al., 2024). This innovative system integrates video tracking, light-detection ranging, and deep learning technologies. FulMAI facilitates comprehensive analysis of natural behaviors exhibited by individual marmosets within their social groups throughout their lifespan, providing insights into behavioral changes during aging or associated with diseases such as AD onset. The FulMAI system will be instrumental in analyzing cognitive functions and uncovering brain-gut interactions in germ-free marmosets.

Furthermore, the team successfully maintained germ-free marmosets until sexual maturity, spanning over two years, culminating in the successful delivery of newborns. This achievement marks the first demonstration that primate fetuses can develop without the effects of maternal microbiota. Additionally, they developed live magnetic resonance imaging (MRI) techniques for germ-free and gnotobiotic animals using a newly developed device. They confirmed that the animals maintained their germ-free status after the MRI Scans. Voxel-based morphometry analysis of brain images revealed reduced volume in the cerebellar regions of germ-free marmosets compared to conventionally housed animals. However, when interpreting these findings, it is essential to consider factors beyond the microbiota, such as human/parental rearing and housing conditions (isolator/open).

Q-core (Tanaka, Sakakibara, Yamamoto, Koyama, Kawaguchi)

The Q-core explored what can be done with current and future quantum computing and how current and future AI should be used to apply quantum computing and other computational technologies to the field of human biology and the microbiome. This year, we conducted causal discovery trials using quantum computing technology, explored the functional activity of the gut microbiome using bioinformatic techniques, and constructed algorithms for quantum computing. In addition, prospects for research using AI were explored.

Kawaguchi (2023) developed a new causal discovery algorithm, qLiNGAM, which applies a quantum kernel to the independence measure of LiNGAM, suggesting that it may be more accurate than existing methods that use the Gaussian kernel, a common conventional kernel, under various conditions in low-data domains (Kawaguchi, 2023, App.1 – 52). Although qLiNGAM can potentially yield novel medical knowledge compared with other causal search algorithms in low-data domains, the data characteristics that would make it useful to apply quantum kernels were unclear. To confirm the usefulness of independence assessment using quantum kernels, we propose a method for estimating mutual information using quantum kernels and investigate its performance in various problem settings, including different sample sizes and different shapes of probability distributions. The results showed that the quantum kernel method performed better than the classical kernel

method when the number of samples was small, the variance was large, or the variables had highly nonlinear relationships (Maeda et al., 2023, App.1 – 85).

Sakakibara, together with PI Sasaki of the Bio-2 core, analyzed the function of the microbiome in the intestinal tract and its application to the common marmoset gut. The results showed that this method allowed the quantification of gene expression levels between intestinal sites, including unknown bacterial genes that were missed by conventional methods. Application of this method to the common marmoset gut revealed that changes in the gut environment can lead to fluctuations in the expression patterns of the microbiome.

Tanaka developed an algorithm to exploit the potential of existing quantum computers. First, Tanaka developed the initial framework of a quantum AI hybrid algorithm to address the complex problem of black box optimization inherent in the field of biology. Second, Tanaka developed a hybrid algorithm for large-scale data optimization using a quantum computer.

Koyama focused on developing project ideas to bridge the gap between Bio Cores and Q Core. Owing to the limited computational capacity of the NISQ machine, identifying suitable applications relevant to Bio Cores is quite challenging. Nevertheless, in a recent announcement, QuERA Computing, founded by physicists from Harvard and MIT, claimed that they would bring 100 logical qubit quantum computers in 2026, which is three years ahead of IBM's most recent roadmap. Based on the discussion of a quantum chemistry expert, we conclude that analysis of biologically relevant molecules in the near term with available algorithms, such as Quantum Phase Estimate (QPE) or Unitary Coupled Cluster Singles and Doubles, (UCCSD) is almost impossible because of the required depth. We will continue to look for other approaches in chemistry that utilize quantum computing.

1-2. Generating Fused Disciplines

* Describe the content of measures taken by the center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1-1. Advancing Research of the Highest Global Level."

Under the leadership of the center director, in FY2023, we prioritized the development of platforms for regular interdisciplinary discussions. To ensure broad participation within the center, as well as easy access for affiliated and guest researchers from overseas satellites and the three graduate schools, we initiated and held biweekly online scientific meetings where all members of the Bio-1, Bio-2, and Q cores participated. The meetings were moderated by the junior principal investigators (Jr PIs), and the discussion section was specifically designed to ensure cross-disciplinary discussions. Additionally, Jr PIs and postdoctoral fellows continued to participate in laboratory meetings of multiple teams.

At the same time, we strived to create new physical spaces where daily in-person interactions and the sharing of laboratory spaces led to the incubation of new interdisciplinary ideas. Specifically, we set up a 400-m^2 open lab unit where our Jr PIs from across cores would work together beginning April 1, 2024, and an approximately 100-m^2 office space where PIs from all campuses can meet under one roof. These measures have led to several cross-disciplinary studies and new collaborations.

Cross-disciplinary studies by young researchers

Microbiome-Quantum computing (Tuganbaev)

The microbiome affects all aspects of human health. Yet we currently lack the tools for modeling microbial ecology. One challenge is that microbiome ecology features higher-order effects where the effect of one bacterium on another depends on the presence of a third microbe. This means that the computational difficulty in modelling such a community increases exponentially as the community size increases. Another challenge is the limitations of classical computer architecture in solving exponentially scaling problems, such as in modeling microbiome ecology. In contrast, quantum computers exploit the phenomenon of quantum superposition to overcome this limitation.

Therefore, the potential of quantum computer applications in microbiome ecology merits further investigation.

Towards this goal, in 2023, we selected a D-wave Advantage quantum annealing computer that features a QPU of more than 5,000 q-bits as the most suitable for a real-world application test among currently available quantum computing systems. Quantum-annealing computers specialize in solving a specialized type of mathematical problem called quadratic unconstrained binary optimization (QUBO). Therefore, we identified a medically relevant microbiome ecology problem that could be formulated as a QUBO and therefore benefit from implementation on a D-wave Advantage quantum annealing computer.

Microbiome ecology plays an important role in infection. The phenomenon of a microbial community preventing a pathogen from invading is termed colonization resistance, and until recently, has been poorly understood. Pioneering studies by Furuichi et al. (under revision at Nature, Honda lab, Keio University) and Spragge et al. (Foster lab, University of Oxford) have recently demonstrated that colonization resistance is, at least to a certain degree, a consequence of competition for nutrients. These studies provide examples of microbial consortia, where members of a microbial community consume the nutrients required by a pathogen, thereby limiting its colonization. This suggests that for a given pathogen, a consortium of commensal bacteria may be found, which may limit its colonization to a certain degree. Such consortia, in the form of live therapeutics, may offer a solution to the growing problem of antibiotic-resistant bacterial infections. However, the manual selection of consortia capable of outcompeting a target pathogen is labor-intensive and presents a bottleneck in the development of such therapeutics. Assuming that accurate data on microbial nutrient utilization can be obtained, we hypothesized that the preliminary selection of candidate consortia for subsequent in vitro and in vivo testing against a given pathogen can be performed in silico, thereby significantly speeding up and increasing the throughput of the therapeutic development workflow. To test this hypothesis, we reformulated the nutrient competition between a pathogen and commensal bacteria with known nutrient utilization profiles as a QUBO and solved it on a D-wave Advantage quantum annealing computer. We found that nutrient competition is mathematically equivalent to a well-known mathematical problem, termed the knapsack problem, with multiple weights. We successfully solved the knapsack problem using multiple weights for a hypothetical pathogen and hypothetical de-colonizing consortia on a D-wave Advantage quantum annealing computer. This suggests that quantum computers may potentially model colonization resistance specifically and the nutrient competition aspects of microbiome ecology. In addition to being affected by nutrients, the microbiome is continuously exposed to xenobiotics, such as drugs. Off-target effects of drugs on the microbiome are currently poorly understood and may have important consequences for human health. Therefore, quantum annealing computers may potentially model microbial nutrient competition and drug-microbe interactions. Such quantum computer models may contribute to the development of live therapeutics against antibiotic-resistant bacterial infections, deciphering the effects of polypharmacy on the microbiome, and fundamentally elucidating microbiome ecology.

In this proof-of-concept study, we relied on the strong assumption that accurate data on the nutrient utilization patterns of pathogens and commensal bacteria could be obtained. Future studies will involve the experimental establishment of methods for the accurate and high-throughput determination of microbial nutrient utilization patterns and the effects of drugs on microbial growth and metabolism.

Microbiome-Neuroregulation (Pan)

The enteric nervous system (ENS) is a complex network of neurons embedded within the walls of the gastrointestinal tract, often referred to as the "second brain" owing to its extensive neural networks and independent function. The ENS plays a crucial role in regulating various gastrointestinal functions, including motility, secretion, absorption, and local immune responses. It

operates autonomously, allowing the gastrointestinal tract to function independently of the central nervous system input. As a diverse community of microorganisms residing in the gastrointestinal tract, the gut microbiota has been increasingly recognized for its role in modulating the ENS function. Because the ENS does not have direct contact with the gut microbiota, these gut microbiota-derived signals are transduced to the ENS via open-type enteroendocrine cells (EECs). As members of the epithelial cell family, EECs receive nutrients or microbial metabolite signals from specialized receptors located on their apical surfaces, which face the intestinal lumen. Upon activation, these receptors initiate intracellular signaling pathways that lead to the release of hormones and neurotransmitters into the lamina propria. These signaling molecules then act on the nearby ENS through paracrine signaling or synaptic connections. Overall, this dynamic and multifaceted bacteria-EEC-ENS process helps to maintain gastrointestinal homeostasis. Dysregulation of this interaction has been implicated in various gastrointestinal and neuropathic diseases, highlighting the importance of understanding the multifaceted crosstalk through which the gut microbiota regulates ENS function.

The Pan group developed an efficient method for dissecting the intact enteric nervous system (ENS) from the mouse intestinal wall, followed by the characterization of the ENS using whole-mount fluorescent immunostaining. Through this approach and gnotobiotic techniques, we found that germ-free mice, which lack gut bacteria, demonstrated significantly heightened colonic neuron activity (~18%) in the ENS compared to healthy SPF mice (~8%). The abnormal neuronal activity due to the lack of gut microbiota indicates that specific gut microbiota that are responsible for inhibiting ENS activity and thus maintaining homeostasis must exist. Meanwhile, we observed that peptide Y (PYY)-producing EECs showed a higher distribution number and larger proportion of open-type morphology in SPF mouse colons. In the other subsets tested (serotonin- or glucagon-producing EECs), this phenomenon was not observed. This finding indicated the potential role of microbiota metabolites in stimulating PYY-producing EECs. The produced PYY then works on ENS neuronal activity and thus maintains ENS homeostasis.

Quantum computing – Functional imaging (Kawaguchi)

As an interdisciplinary study in FY2023, we applied the causal discovery algorithm to all brain activities of mice captured by fMRI to search for causal relationships among brain regions. Using brain images stored in the Brain Imaging Data Structure format, where the CA1 region was activated by optogenetics, a causal discovery algorithm was performed after setting the region of interest. Specifically, focusing on to 5–7 regions of interest in the limbic system, a causal discovery algorithm was applied to the first principal component obtained from principal component analysis of the brain image data of each region of interest. A diagram with arrows drawn from the CA1 region to other regions of interest was expected to be the output. When the conventional causal discovery algorithm was used, the CA1 region was the top node. The qLiNGAM outputs a diagram with arrows drawn in the CA1 region. The results suggest that the hyperparameters related to the design of quantum kernels, such as the depth and number of qubits, need to be adjusted.

Collaborations between cores:

Bio-2 Core - Bio-1 Core (Sato, Honda, Atarashi)

In FY2023, the Sato team collaborated with the Honda and Atarashi teams (Bio-1) to explore the barrier function of the intestinal mucin layers against gut microbes. We used pks+ E. coli, which produces the DNA-damaging toxin colibactin, and analyzed the accumulation of somatic mutations in the host colonic epithelium. The team established an in vitro culture system and gnotobiosis to model host-bacterial interactions and found that the mucin layer played a central role in protecting the colonic epithelium from colibactin-induced DNA damage. Further studies will be conducted within these collaborative teams to investigate the stress signaling pathways that regulate mucin barrier function and seek preventive measures to reduce colibactin-induced DNA damage.

The Sato team also initiated a collaboration with the Arita team (Bio-1) to screen for gut microbe-derived metabolites that interact with the host colonic epithelium. This collaboration will be extended

to incorporate a gnotobiotic mouse model (Honda and Atarashi teams), neuroregulation model (Yuzaki team), and human tissue analysis (Suematsu and Hishiki teams).

Collaborations to build joint analytical platforms and databases:

Metabolome Team (Arita, Soga)

The cutting-edge technologies of the Metabolome Team, which widely cover both hydrophobic and hydrophilic metabolites, will be applied to the metabolite-based approach for a detailed mechanistic understanding of the microbiota-mediated maintenance of homeostasis and multiorgan systems in the WPI-Bio2Q program. In 2023, Arita group has started to develop a microbiome lipidome atlas (database) based on a series of isolated bacterial cultures combined with genome sequence data. Additionally, we developed a strategy for isolating genes encoding lipid biosynthetic enzymes from specific lipid-producing bacteria. We also introduced a GPCR screening system developed by Dr. Asuka Inoue group at Tohoku University to identify potential receptors expressed in host cells and tissues. To verify the structure-activity relationship of functional lipids and the causal relationship with the obtained phenotype, lipids, including structural isomers, were chemically synthesized and subjected to various assays in collaboration with the Bio-2 Homeodynamics Mechanistic Analysis Core. In addition, we set up MALDI-based imaging mass spectrometry to visualize the distribution of bacterial lipids in tissues and cells and will collaborate with the Bio-2 Imaging Metabolomics Team.

The Soga group has the world's largest polar and charged metabolome analysis platform with over 60 metabolome analysis instruments, including CE-MS, LC-MS, GC/MS, IC-MS, SFC-MS, and NMR. To promote collaboration among researchers in various fields, Soga Lab assists with metabolome analysis free of charge and has measured more than 10,000 samples by 2023.

Genome Dynamics Team (Siomi, Ishigaki, Solberg)

Human health is maintained through complex interactions between the microbiome and host genetics, which have for the most part not been comprehensively elucidated. The ultimate goal of the Genome Dynamics Team was to elucidate the mechanisms by which host genetic factors control the immune system in the context of various microbiomes. The first essential step for achieving this goal is to establish the experimental system for accurate and comprehensive evaluation of genetic components and establishing the bioinformatics technique to evaluate genetic association with various molecular phenotypes, and the Genome Dynamics Team's current focus is to achieve this. Single-nucleotide polymorphisms (SNPs) and transposable elements (TEs) are major genetic factors that play essential roles in defining inter-individual differences in genomic sequences. Recent studies demonstrated that transposable elements (TEs) can substantially affect the genetic risk of common human diseases (Kojima et al., 2023, App.1 – 64) and promote homeostatic and inflammatory responses in the microbiota (Lima-Junior et al., 2021). The Siomi team has been investigating the biological mechanisms of TEs and the Ishigaki team has identified risk SNPs for various immune-related human diseases. Ishigaki et al. conducted bioinformatics research to investigate the interactions between autoimmunity-risk single nucleotide polymorphisms (SNPs) and the epigenome, transcription factor activities, gene expression, and splicing in various immune cells. The Siomi team has bioinformatics expertise in investigating transcribed TEs, which have been frequently missed in previous transcriptome studies. Therefore, joint efforts within the Genome Dynamics team enabled us to investigate the majority of genomic factors and test their association with various molecular phenotypes.

The next step for the Genome Dynamics Team is to collaborate with other teams to provide accurate molecular phenotype information reflecting microbiome biology (e.g., microbiome-derived metabolites) and to evaluate genetic control over such phenotypes. All these research activities contribute to elucidation of the functional underpinnings of human immunity and host-microbiome interactions.

Human Disease Analysis Team (Seki, Yoshino)

As detailed in 1-1, the human disease analysis team organically increased the number of stool and plasma samples for all our ongoing studies, with a special emphasis on advancing microbiota assessments in Parkinson's disease.

Metabolome Imaging Team (Suematsu, Hishiki)

In FY2023, we collected data on numerous metabolites detected by imaging mass spectroscopy and surface-enhanced Raman imaging using postoperative clinical samples of breast and pancreatic cancers. We focused on these malignancies owing to two intriguing backgrounds. First, the two cancers share important pathologic changes such as chronic inflammation and regional fibrosis. Secondly, previous studies suggest that there was evidence of the presence of "intracellular bacterial infection" in the background of chronic inflammation associated with these cancers.

In needle-biopsied frozen samples collected from patients with breast cancer, we successfully imaged different reactive sulfur species and demonstrated the usefulness of profiling these metabolites to differentially diagnose ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC); polysulfides that were detected at 480 cm-1 in cancer stromal regions serve as a hallmark for diagnosing IBC, and account for the biomarker of desmoplastic reaction in the breast cancer. However, we discovered that the Protein Arginine Methyltransferase type 1 (PRMT1) serves as a critical player that methylates three glycolytic enzymes (PFKFB3, PKM2, and PHGDH) in triple-negative breast cancer (TNBC) to convert glucose preferentially towards the serine-glycine cleavage system to provide methyl units to cancer cells and thiols to cancer stroma to enhance chemoresistance. We identified the post-translational methylation of these enzymes in TNBC, revealing new molecular targets for improving chemotherapy.

In postoperative pancreatic cancer tissues, polysulfides were abundantly present in both cancer cells and the surrounding stoma, serving as a determinant of the overall postoperative prognosis. Notably, only small amounts of polysulfide-generating enzymes (cystathionine beta-synthase and gamma-lyase) have been detected in both IBC and pancreatic cancers. In pancreatic cancer tissues, cancer-associated fibroblasts serve as the major source of cystathionine gamma lyase. Accordingly, we need to further examine whether intracellular pathogens (bacteria or fungi) contribute to the generation of polysulfides.

Future directions: Q core - Bio Cores

Harnessing the power of AI rather than waiting for the advent of useful quantum computing would be ideal. To accelerate the identification of unknown metabolites, Koyama developed a transformer called the Gut microbiome Metabolite Prediction Transformer (Gut-MPT), which predicts metabolites from given reactants and enzymes (future collaboration with the Bio-1 core). Using the predicted metabolites, MassFormer, developed at the University of Toronto, was used to predict the mass spectra to match the experimental data.

Koyama is also investigating a potential project employing Quantum AI in the field of brain organoids (future collaboration with the Bio-2 core). AI was trained in various skills, such as language, spatial recognition, and simple mathematics, then used to train brain organoids of various genetic backgrounds to observe issues under the influence of neurotransmitters. Quantum AI might be ideal for processing signals from brain organoids owing to its high-dimensional nature.

2. Global Research Environment and System Reform

2-1. Realizing an International Research Environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:

- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- Proactive efforts to raise the level of the center's international recognition and to obtain diversity within the center including gender balance.
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

Recruiting and Hiring Researchers and Research Support Personnel

Creating an authentic international environment is imperative to attracting and retaining top talent

from diverse backgrounds worldwide. Recruiting international researchers and English-speaking administrative personnel is crucial as it enables the center to fully leverage its diversity and achieve cohesiveness and synergy. In FY2023, we continued to actively emphasize the WPI missions of globalization and diversity in all open calls, and the international recruitment of researchers was widely published on the Center's website, Nature Careers, the Career Center webpage of the Association for Women in Science, and social media platforms such as LinkedIn and X (Twitter). Consequently, a scientist with expertise in quantum computing was hired as the first PI from an overseas company, and two international female researchers joined the center as postdoctoral fellows. In total, we welcomed one PI and six Jr. PIs, two postdocs, three advisors, and nine affiliated PIs. In addition, four research support staff members fluent in English were hired this fiscal year, and three or more will be hired as of April 1, 2024.

Efforts to Attract Young Researchers

To attract and support world-class researchers, WPI-Bio2Q has implemented a globally competitive salary structure, as well as internal policies for relocation allowances and start-up funds. These efforts have resulted in the successful recruitment of young researchers worldwide.

In FY2023, WPI-Bio2Q made efforts to internationalize the research environment. This includes providing funding information in English and expanding support systems for grant applications in the Japanese academic system. WPI-Bio2Q also promoted the translation of documents, contracts, and training courses that are mandatory for researchers (e.g., genetic recombination training courses at the School of Medicine).

The Center and the host institution worked together to provide relocation and living support services (including visa applications) for international researchers joining WPI-Bio2Q. As a center-driven initiative, we have created an Onboarding Handbook for WPI-Bio2Q researchers. We plan to adapt and gradually expand the future versions for use by other international researchers at Keio University. To promote young researchers, we launched the STaMP program (see 3-2 for details), to which enrolled 14 domestic and international graduate students.

Ensuring Diversity, including Gender Balance

The center proactively invited female scientists to participate in all events, including symposiums and workshops. For example, the Bio2Q Science Meeting series launched this fiscal year to promote research presentations and collaborative scientific discussions and has achieved up to 52% female participation among center researchers, university faculty, staff, and students.

To better understand the challenges faced by female researchers and explore potential solutions, Administrative Director Sampetrean participated in the FY2023 mentoring program for female researchers organized by the Office for the Promotion of a Collaborative Environment, which is responsible for promoting diversity throughout Keio University. In FY2024, we plan to collaborate further with the Office for the Promotion of a Collaborative Environment and establish a mentoring system for female scientists within Bio2Q.

Members are encouraged to continuously educate themselves on the benefits of diversity and inclusion through seminars, shared articles, and relevant reading materials. Additionally, the Center promotes diversity and emphasizes the importance of respecting individuality by providing information on harassment prevention.

2-2. Making Organizational Reforms

* Describe the system reforms made to the center's research operation and administrative organization, along with their background and results.
* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Describe the center's operation and the host institution's commitment to the system reforms.

Development of Internal Rules and Research Support System

In a university-wide effort to comprehensively support world-class international research, the host

organization Keio University utilizes a system consisting of three departments: the "Office for Research Coordination and Administration" to support the promotion of research activities; the "Office of Innovation and Entrepreneurship" to promote the social implementation of research results through industry-academia-government collaboration and provide startup support; and the " Keio University Global Research Institute (KGRI)" to serve as the parent organization for various interdisciplinary research projects. In FY2023, the university amended its internal regulations to formally position Bio2Q as a specially designated, advanced international research center within the KGRI and supported the center's activities at the university level.

To reinforce support for research activities, the host organization recruited four University Research Administrators (URAs) with a strong background in research and industry collaboration with the Office of Innovation and Entrepreneurship. These URAs hold joint positions with Bio2Q, provide comprehensive support, and work closely with researchers at the center throughout the research process.

In turn, Bio2Q has drafted and implemented more than ten internal regulations for the center, such as regulations regarding the organization of the Human Biology-Microbiome-Quantum Research Center, Internal Regulations, and Bylaws for PIs and Jr. PIs, internal regulations for researchers and senior researchers, internal regulations for faculty appointment and promotion committees, and internal regulations on handling research start-up support funds. These internal regulations are associated with the internal regulations of Keio University in such a way as to allow the promotion of reforms in both directions.

Reform of the management system

To increase the transparency, efficacy, digitalization, and globalization of the center's operations, Bio2Q implemented an industry-modeled, WPI-mission-centered project management system in English. The administrative division, including its two directors, two advisors with expertise in organizational startup and WPI center administration, and members of the Academic Research Support Department from Keio Headquarters met weekly to review and implement these projects. Biweekly meetings with administrative managers and staff in charge of Bio2Q at the Faculties of Medicine, Pharmacy, and Science and Engineering were instrumental in sharing information, uncovering organizational challenges, exploring the potential for reform, and coordinating overall activity with the host organization.

3. Values for the Future

3-1. Creating and Disseminating the Societal Value of Basic Research

* Describe the content of measures taken by the center to widely disseminate the results of its basic research to the general public.
* Describe what was accomplished in the center's outreach and other activities last year and how they have contributed to creating the Societal Value of Basic Research. In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.

Outreach Activities

Website updates and promotional materials: To attract scientists and students worldwide, the WPI-Bio2Q news section of the website is updated four times a month. Additionally, we have developed and distributed various promotional materials, including one digital/printable donation brochure for stakeholders and four digital/printable research introduction brochures for young researchers. Leveraging Keio University's integrated education system, WPI and Bio2Q brochures were distributed to Keio Elementary and Middle Schools.

Media exposure: On May 19, 2023, the Japan Times introduced WPI-Bio2Q to the global public under the title "Sustainability a key focal point of education and research" and described Bio2Q's identity of using both quantum computing and conventional bioanalytical methods to elucidate the relationship between the microbiome and human health.

Social media outreach: Through our WPI-Bio2Q account on LinkedIn (SNS), we proactively reported WPI-Bio2Q activities and job openings and sent direct messages to scientists in related

research fields. As a result, we formed a network of 844 scientists, including research students and professionals, from around the globe, with some followers expected to apply for the WPI-Bio2Q postdoctoral fellowships and Research Internship Program.

Symposia and events: The Keio University WPI-Bio2Q 2nd Symposium was held onsite/online at the Keio University Shinanomachi Campus in Tokyo, Japan, on July 27, 2023, with sessions by ten of the world's top scientists from Harvard University (USA), MIT (USA), MRC Laboratory of Molecular Biology (UK), and Keio University. In total, 186 scientists participated onsite/online, including 135 from Japan, 19 from the USA, 5 from India, 3 from Italy, 2 from Singapore, and 22 from other countries (119 men and 67 women). Global participants engaged in lively discussions on achieving good health and longevity in society through the integration of human biology, microbiome, and quantum computing. These discussions explored the potential of these fields to drive advancements in the life sciences.

Additionally, WPI-Bio2Q invited top international scientists from the Icahn School of Medicine at Mount Sinai, USA; Harvard Medical School, USA; University of Pennsylvania, USA; and Springer Nature, Germany to hold eight open scientific seminars at the center, facilitating in-person knowledge exchange with a broad audience. The international symposium, co-hosted with the Cancer Convergence Education Network and organized in Shinanomachi, gathered promising early career scientists who actively discussed their latest research results and trends in the field. WPI-Bio2Q was exhibited at the Metabolome Symposium 2023 in Japan to introduce WPI and Bio2Q to 400 attendees from academia and industry.

Finally, nine Bio2Q internal scientific meetings were held to comprehensively elucidate intramural research and accelerate interdisciplinary and fusion projects.

3-2. Human Resource Building: Higher Education and Career Development

* Describe the content of measures taken by the center to foster young researchers, including doctoral students, through their participation in a research system that creates new interdisciplinary domains within a rich international environment.

WPI-Bio2Q has established a joint interdisciplinary graduate English program called Science and Technology and Medicine, Pharmacy (STaMP) between the Graduate Schools of Medicine, Pharmaceutical Sciences, and Science and Technology. The WPI-Bio2Q STaMP program aims to create a “place of resonance” where faculty, researchers, and students from three graduate schools can interact directly, and where each graduate student works with multiple mentors to receive guidance across graduate school boundaries.

Students in this program are also designated WPI Research Assistants (RAs), allowing them to work as part-time researchers and receive a monthly stipend. This system allows students to actively engage in research and participate in activities and exchanges across the three graduate schools. Upon completion of certain requirements, including participation in events organized by WPI-Bio2Q (such as presentation workshops, open seminars, and retreats), students will receive a StaMP program certificate of completion along with a degree from their affiliated graduate school. Students may be mentored and placed in the laboratories of WPI-Bio2Q PIs and affiliated PIs. In FY2023, nine affiliated PIs from three graduate schools were appointed in connection with the STaMP program.

In FY2023, 14 students, mostly current graduate students, were enrolled in the StaMP program and designated as WPI RAs. The program aims to recruit WPI RAs from abroad through the newly established research internship system. Selected applicants will receive round-trip travel expenses and a daily stipend to conduct research for up to eight weeks under the supervision of several WPI-Bio2Q PIs. Eight applications have been received for the FY 2024 internship.

STaMP organized the second "Presentation Skills Lecture/Workshop 2023,” which aimed to

improve the research presentation skills of young researchers, particularly graduate students. After the one-day lecture, the workshop was conducted in small groups consisting of a tutor and four or five participants over the following four days. To facilitate an active exchange between researchers and students in the STaMP program, we plan to hold the first scientific retreat in the first half of FY2024. The retreat will be attended by PIs, Affiliated PIs, Jr. PIs, post-docs, and WPI RAs.

3-3. Self-sufficient and Sustainable Center Development

* Describe the state of implementation of the host institution's mid-to-long term measures for supporting the center toward becoming self-sufficient and sustainable after the 10-year funding period ends, such as reforming the host institution's organization, providing personnel with priority allocation of tenured posts to the center, providing fundamental financial support, and material support including land and buildings.

To support Bio2Q in achieving self-sufficiency and sustainability, the host organization and Keio Headquarters are implementing several strategic measures. These measures include declaring the center as a special research zone, prioritizing the allocation of indirect expenses through the university's internal regulations, and establishing special regulations for the age-independent recruitment of excellent researchers. Keio University is also introducing previously unaddressed measures such as a PI personnel expense system and a buyout system, striving to improve researchers' motivation and secure valuable time for research.

To meet the significant challenge of securing research space "under one roof, the executive team of Keio University, including the President and Vice President have started securing funds, including large donations. In addition to such donations, which sometimes entail restrictions related to donor policies, negotiations with the Ministry of Education, Culture, Sports, Science and Technology (MEXT) for additional funding are also underway. Keio University is committed to establishing research facilities for Bio2Q in 2027, by utilizing both private and public funds.

4. Others

* In addition to the above 1-3 points, if there is anything else that deserves mention regarding the center project's progress, please note it.

5. Center's Response to Results of Last Year's Follow-up

* Transcribe the item from the "Actions required and recommendations" section in the site visit report and the Follow-up report, then note how the center has responded to them.
* If you have already provided this information, indicate where in the report.

Actions required and recommendations

1) The life science of Bio2Q is going extremely well. Individual research initiatives, including those of microbiome, organoid, lipidomics, synapse neurobiology and gene-engineered marmosets, are at world-leading levels. What is highly expected in the near future is to bring all of these initiatives together and to enhance fusion by having each Bio2Q member share the vision of director Honda. The center director will need to continuously help foster interactions during center operations by pointing out where collaborative connections still need to be established. Moreover, it is important to develop experimental and analytical techniques to understand the interactions between humans and microbiome at the molecular level. Furthermore, a data management plan for sharing data acquired from the center and the satellites would be helpful for future advancement.

To help foster interactions and enhance collaborative connections within the center, we enlisted two senior scientists as liaisons between the biology and computational science groups. Furthermore, as an initial platform for sharing the vision of the center director with each member and promoting fusion research, we started biweekly scientific meetings focused on collaborative dialogues among PIs and Jr PIs.

Significant emphasis has also been placed on the training of young scientists. All PIs participated in the selection process, which involved presentations and interviews for our postdoctoral and Jr PI candidates. Each post-doctoral fellow or STaMP graduate student was co-mentored by at least two PIs from different cores. We strongly encourage postdoctoral fellows and graduate students to regularly attend laboratory meetings with their co-mentors to exchange ideas. In addition, they were encouraged to participate in meetings and workshops on a wide range of topics in different

disciplines. Access to these training opportunities will endow graduate students and postdoctoral fellows with the important skills needed to become key drivers of fusion research.

Creating robust systems for data sharing and management as early as possible is crucial for the growth of Bio2Q and for integrated data and resource utilization among the three cores, affiliated facilities, and satellites. While we are currently leveraging the platforms provided by Keio University, we are also developing a blueprint for a center-oriented data management platform. We are also actively seeking a URA to oversee the data management responsibilities.

2) Fusion of microbiome biology and quantum computing is still in its infancy and in a very challenging direction. But it will be a valuable challenge to tackle. To apply quantum computing to life science problems will require further advances in quantum computers combined with deep analyses on how problems can be solved. Finding practical but biologically relevant problems and solving them using quantum-inspired calculation is a good way to proceed. The commitment of both computational scientists and biologists is needed for this to succeed. Recruiting researchers from outside Bio2Q could be instrumental in bridging the biology cores and the quantum computing core. Moreover, it is important to keep open the possibility of adjusting or even revising the roadmap in light of external developments, such as new advances in quantum computing in coming years and good usages of a hybrid-type computer.

As mentioned in Section 5.1, in response to this recommendation, in December 2023 and January 2024, we recruited two senior scientists instrumental in bridging biology and quantum computing cores. Based on extensive discussions since they joined, we began to formulate a plan. The roadmap outlined below will be adjusted to match external developments in accordance with the recommendations.

The deployment of a quantum computer at Bio2 will begin in 2026 at the earliest owing to the availability of quantum hardware. The currently available Noisy Intermediate-Scale Quantum computer (NISQ) has limitations in achieving quantum advantages. An error-corrected machine that enables us to attain quantum advantages is expected to become available in 5 years.

We also asked how quantum computing and related technologies, such as generative AI, can be applied in biological studies to accelerate speed and quality. Until the advent of these quantum machines, we focused on generative AI technology to accelerate scientific research. Simultaneously, we will keep a close eye on the advancement of quantum-computing technology applied to the life sciences.

It takes more than half a year, or 1 year, to circle around a biological study with 1) hypothesis generation, 2) biological experiments, 3) interpretation of results, and 4) creation of new knowledge and laws of biology, as biological phenomena contain considerable variations, such as materials, metabolomes, and multiorgan networks.

Recent generative AI studies have focused on human communication matters and knowledge of specialized science areas, and are effective in analyzing and predicting complex subjects using specialized data. We propose the application of generative AI to hypothesis prediction for biological studies to shorten the study cycle and improve the quality of the study. We are currently selecting the study projects and initiating research activities.

As ideas for utilizing quantum computing in future studies, we are investigating and selecting candidate studies, such as the multi-omics analysis of complex biological matter and super parallel computing in biology.

3) Bio2Q aims to achieve the WPI goal of 20% non-Japanese PIs and 30% non-Japanese researchers in total. We encourage the center to take every possible measure to realize this goal. Bio2Q also aims to achieve 50% female researchers. This is a lofty goal which will require a strong, strategic recruitment plan. It is also not too early to begin planning career enhancement services for junior researchers to advance their future career development.

We value diversity within our organization by recognizing its crucial role in fostering innovation and

progress. We are committed to establishing a center that embraces diversity on an international scale.

To achieve the WPI goal of 20% non-Japanese PIs and 30% non-Japanese researchers, Bio2Q is dedicated to attracting and supporting top-tier talent worldwide. We have already implemented several measures to facilitate the integration of global researchers into the community. Specifically, we offer globally competitive salaries and establish a comprehensive support system that is tailored to the needs of international researchers. This includes assistance with relocation and living in Tokyo as well as contractual and procedural support. Additionally, we provided research-related assistance, such as English versions of university-mandated training courses and a detailed onboarding handbook. Communication with our international researchers was conducted exclusively in English, and several laboratories held meetings conducted in the same language, ensuring collaboration and inclusivity across our diverse team.

To meet our goal of having 50% female researchers, our specific measures include recruitment, support, and career development. We first assessed our recruitment system and identified steps that could be improved to attract female scientists. We set an initial milestone of 40% and expanded our open calls to advertisements for women in STEM initiatives and scientific women's associations. Furthermore, we will implement specific measures, such as a clear and transparent pathway for advancement, flexible work arrangements, and leadership development opportunities tailored to female scientists.

Bio2Q actively facilitates career advancement for researchers. We support the transition of senior postdocs into independent Jr PIs and that of Jr PIs into senior PIs. We offer an independent research environment and concrete career path that empowers junior researchers to progress to senior positions after a comprehensive review process. To further support the growth and success of our junior researchers, we established a mentoring system to assist them in obtaining grants. Our objective was to provide all the necessary resources and guidance to ensure professional advancement and a smooth transition into leadership roles within our institution.

4) The host university should develop a strategy in the next year on how it will support Bio2Q after WPI program funding ends. Establishing an independent and autonomous research center is a new experience for Keio University. It is crucial to form a consensus on how Bio2Q will contribute to advancing the internationalization of Keio University, enhancing the university's global visibility, and delivering benefits to the university as a whole. The president and top management of Keio University should provide strong support in this effort.

Regarding the establishment of a physically independent building, ongoing plans to establish new research facilities for Bio2Q are detailed in 3-3.

In FY2023, Keio University was selected to obtain funding from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) through the Program for Forming Japan's Peak Research Universities (J-PEAKS). The host institution will leverage this opportunity to further promote large-scale projects, such as the WPI and COI-NEXT initiatives, and, in turn, use these as models to launch several other top-level world research bases, thus creating a positive feedback loop between Keio University and Bio2Q. Specific initiatives include enhancing the international visibility of Keio's research content and achievements through the construction of a research showcase by the KGRI, internalizing research and researchers through collaboration with the Okinawa Institute of Science and Technology Graduate University (OIST), a collaborating university in J-PEAKS, and strengthening research support systems and globalization through enhanced collaboration with overseas participating universities.

Furthermore, Keio University will increase its support for Bio2Q through the Office of Innovation and Entrepreneurship and URAs from the Departments of Open Innovation, Startups, and Intellectual Property. Keio University will also work towards the realization of an ecosystem through the promotion of international collaborative research and contributions to society. The host

organization will also rely on feedback from the center and promote reforms in Keio's Administrative Office for Academic Research Support to improve the university’s overall research support services to meet global standards.

Appendix 1 FY 2023 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2023. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.
   A. WPI papers
      List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state "WPI" and the name of the WPI center (WPI-center name)). (Not including papers in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)
   B. WPI-related papers
      List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

      Note: On 14 December 2011, the Basic Research Promotion Division (the Basic and Generic Research Division at present) in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. From 2012, the authors' affiliations must be clearly noted.

(2) Method of listing paper
   - List only refereed papers. Divide them into categories (e.g., original articles, reviews, proceedings).
   - For each, write the author name(s); year of publication; journal name, volume, page(s) (or DOI number), and article title. Any listing order may be used as long as format is consistent. (The names of the center researchers do not need to be underlined.)
   - If a paper has many authors (say, more than 10), all of their names do not need to be listed.
   - Assign a serial number to each paper to be used to identify it throughout the report.
   - If the papers are written in languages other than English, underline their serial numbers.
   - Order of Listing
      A. WPI papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles

      B. WPI-related papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles

(3) Submission of electronic data
   - In addition to the above, provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
   - The papers should be divided into A or B categories on separate sheets, not divided by paper categories.

(4) Use in assessments
   - The lists of papers will be used in assessing the state of WPI project's progress.
   - They will be used as reference in analyzing the trends and whole states of research in the said WPI center, not to evaluate individual researcher performance.
   - The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents
   - After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

A. WPI papers

1. Original articles

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metabolism; has the *Entamoeba* lipid metabolism network evolved through gene loss and gain to enable parasitic life cycle adaptation?", *mSphere 8* (5), doi: 10.1128/msphere.00174-23, (2023)

2. Review articles

N/A

3. Proceedings

N/A

4. Other English articles

N/A

B. WPI-related papers

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3. Proceedings

N/A

4. Other English articles

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86) Ueda M, Okahashi N, Arita M., "Chapter 27: Microbial Lipidomics", *Mass Spectrometry for Lipidomics: Methods and Applications* (Holcapek M., Ekroos K. eds.), pp. 689-704, Willey-VCH, Weinheim, (2023)

2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY 2023 in order from most recent.
- For each, write the date(s), lecturer/presenter's name, presentation title, and conference name.

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
2024/2/19	Kenya Honda	Human Microbiota Regulation of Barrier Immunity	KEYSTONE SYMPOSIA on Molecular and Cellular Biology "Regulation of Barrier Immunity (X8)" Banff, AB, Canada
2024/2/16	Erika Sasaki	Development of Alzheimer's Disease Models in Marmosets Through Genome Editing	Cambridge University Biological Society, University of Cambridge
2023/11/8	Jun Huh	Unraveling regulation and unexpected role of Interleukin-17.	NIH-FDA Immunology Interest Group (IIG). Bethesda, MD, USA
2023/10/4	Toshiro Sato	Biological understanding of patient-derived cancers using organoid technology	VIB conference Tumor Heterogeneity, Plasticity and Therapy, Leuven, Belgium
2023/10/2	Makoto Arita	Introduction of the JST-ERATO Lipidome Atlas Project in Japan	International Congress on the Bioscience of Lipids (ICBL2023): Palma de Mallorca, Spain
2023/9/7	Makoto Suematsu	Imaging metabolomics to decipher cancer metabolism	Keynote Lecture, Material Sciences, Singapore

2023/9/3-6	Haruhiko Siomi	"Transposable elements at the crossroads of evolution, health and disease,"	Keystone meeting Whistler, British Columbia, Canada
2023/7/23	Sloan Devlin	Human Gut Bacteria Produce Anti-Inflammatory Metabolites	Invited talk, Japan Agency for Medical Research and Development (AMED) Moonshot symposium, Healthy longevity through the control of the chronic inflammation Chiyoda Ward, Tokyo, Japan
2023/5/3	Daniel Mucida	Immunity and tolerance in the gut	American Association of Immunologists Major Symposium, USA
2023/1/8	Michisuke Yuzaki	Regulation of Neuronal Function by Extracellular Scaffold Proteins	US-Japan Joint Workshop on the Neurovascular Unit 2023, Keio University, Japan

3. Major Awards

- List up to 10 main awards received during FY 2023 in order from the most recent.
- For each, write the date issued, the recipient's name, and the name of award.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
2023/12/2	Therese Solberg	Dr. Lutz and Dr. Celia Zwillenberg Prize, University of Bern
2023/11/15	Kenya Honda	Highly Cited Researcher 2023, Clarivate Plc, USA/UK (Immunology)
2023/11/15	Toshiro Sato	Highly Cited Researcher 2023, Clarivate Plc, USA/UK (Molecular Biology and Genetics)
2023/11/15	Koji Atarashi	Highly Cited Researcher 2023, Clarivate Plc, USA/UK (Immunology)
2023/11/10	Sloan Devlin	Grinnell Fund for Biomedical Research, Harvard Medical School, USA

2023/11/3	Michisuke Yuzaki	Medal of Honor, Japan (Medal with Purple Ribbon)
2023/11/1	Kazuyoshi Ishigaki	Medical Research Encouragement Prize of The Japan Medical Association, Japan
2023/9/23	Makoto Suematsu	Nishimaru-Tsuchiya International Award, 12th World Congress for Microcirculation, Beijing, China

Appendix 2　FY 2023 List of Principal Investigators

NOTE:

*Underline names of principal investigators who belong to an overseas research institution.

*In the case of researcher(s) not listed in the in the latest report, attach a "Biographical Sketch of a New Principal Investigator"(Appendix 2a).

*Enter the host institution name and the center name in the footer.

<Results at the end of FY2023> **Principal Investigators Total: 16**

Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center director Kenya Honda	55	Professor, Keio University School of Medicine	M.D., Ph.D. Microbiome, Immunology	90	November 11, 2022	Usually stays at the center	
Toshiro Sato	51	Professor, Keio University School of Medicine	M.D., Ph.D. Gastroenterology	90	November 11, 2022	Usually stays at the center	
Makoto Arita	54	Professor, Keio University Faculty of Pharmacy	Ph.D. Lipid biology, Lipidomics	80	November 11, 2022	Usually stays at the center	
Shu Tanaka	43	Associate Professor, Keio University Faculty of Science and Technology	Ph.D. Quantum annealing, Statistical mechanics, Computational physics	80	November 11, 2022	Usually stays at the center	
Haruhiko Siomi	64	Professor, Keio University School of Medicine	Ph.D. Epigenetics	90	November 11, 2022	Usually stays at the center	
Michisuke Yuzaki	64	Professor, Keio University School of Medicine	M.D., Ph.D. Neuroscience, Synaptopathy	90	November 11, 2022	Usually stays at the center	
Jun Huh	50	Associate Professor, Department of Immunology, Harvard Medical School, Harvard University	Ph.D. Microbiome and Neuroimmunology	10	November 11, 2022	Usually stays at home institution and attends meetings online	Attended the Bio2Q Symposium and delivered an online presentation

Erika Sasaki	57	Director, Department of Marmoset Biology and Medicine, Central Institute for Experimental Animal	Ph.D. Laboratory animal science, Reproductive biology	80	November 11, 2022	Usually stays at the center	
Yasuyo Minagawa	53	Professor, Keio University Faculty of Letters	Ph.D. Developmental cognitive neuroscience, Developmental psychology, Psycholinguistics	80	November 11, 2022	Usually stays at the center	
Radu Aricescu	51	Programme Leader, Neurobiology Division, MRC Laboratory of Molecular Biology	Ph.D. Neuroscience & Structural Biology	TBD	November 11, 2022	Usually stays at home institution and attends meetings online or onsite	Attended the Bio2Q Symposium and delivered a presentation Attended meetings for laboratory setup
Tomoyoshi Soga	64	Professor, Keio University Faculty of Environment and Information Studies	Ph.D. Analytical chemistry, Metabolomics, Cancer metabolism	80	November 11, 2022	Usually stays at the center	
Naoki Yamamoto	47	Professor, Keio University Faculty of Science and Technology	Ph.D. Quantum computation, Quantum control	80	November 11, 2022	Usually stays at the center	
Yasubumi Sakakibara	63	Professor, Keio University Faculty of Science and Technology	Ph.D. Bioinformatics	80	November 11, 2022	Usually stays at the center	
Makoto Suematsu	66	Director, Live Imaging Center, Central Institute for Experimental Animals / Professor, Keio University School of Medicine	M.D., Ph.D. Biochemistry	80	November 11, 2022	Usually stays at the center	
George Augustine	68	Professor, Temasek Life Sciences Laboratory, National University of Singapore	Ph.D. Neurobiology	30	November 11, 2022	Usually stays at home institution and attends meetings online or onsite	Conducted presentation skills seminar and provided tutoring at the center Attended the Bio2Q Symposium and delivered an online presentation
Takahiko Koyama	52	Professor, Keio University Bio2Q	Ph.D. Physics	100	January 1, 2024	Usually stays at the center	

*Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Principal investigators unable to participate in project in FY 2023

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age) Takahiko Koyama (52)

Affiliation and position (Position title, department, organization, etc.)

Professor, Keio University Bio2Q

Academic degree and specialty Ph. D. in Physics

Effort 100 %

* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history

Research:

01/2024-	**Principal Investigator**, Human Biology-Microbiome-Quantum Research Center, Keio University
08/2014-01/2024	**Research Staff Member,** IBM Corporation, TJ Watson Research Center IBM Research, USA
01/2012-08/2014	**Research Scientist**, IBM Japan
12/2009-12/2011	**Business Development Manager**, IBM Japan
10/2007-11/2009	**Managing Consultant**, IBM Japan
12/2003-09/2007	**Senior Scientist,** Takeda Pharmaceutical Company Discovery Research Laboratories, Pharmaceutical Research Division
11/2002-10/2003	**Academic Visitor,** Sir William Dunn School of Pathology University of Oxford
01/2002-10/2003	**Postdoctoral Fellow**, Department of Pathology University of Pennsylvania
09/1999-09/2001	**Business Development Analyst**, Business Development Department Oracle Japan

Education:

Ph. D. in Physics, Department of Physics, Cornell University

Concentrations: Elementary Particle Physics

Advisor: Dr. Richard Talman Date Awarded: August 23, 1999

B.S. in Physics, Department of Physics, Georgia Institute of Technology

Date Awarded: June 1994

Achievements and highlights of past research activities

At Takeda Pharmaceutical I engaged in optimizing lead compounds in ten drug discovery projects, each addressing critical aspects of cancer or central nervous system disorders. In two projects, the compounds progressed to Phase I clinical trials, TAK-960 targeting PLK1 was designed to bind back pocket of the kinase accommodating induced-fit. Furthermore, I delved

into the field of machine learning, contributing to the design of a High Throughput Screening Library.

At IBM Watson Research Center, I paved the way for genomic medicine, laying the groundwork for Watson for Genomics by leading research scientist across the globe. With the collaboration of New York Genome Center, we have published two papers on glioblastoma clinical trials. In the very early phase of COVID-19 pandemic, with the development of genome analysis software from scratch, I could publish a preprint titled 'Variant Analysis of COVID-19 Genome' ahead of Chinese Academy of Science. The paper revealed the existence of two distinct clades, estimated speed of mutations, and potential multiple introductions into human. The preprint paper was later revised with updated genome data and published in WHO Bulletin. Also, I have discovered and reported a rapidly spreading strain with spike D614G mutation, which might affect vaccine strategy. Besides these two papers, I have published various papers on the topic.

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Recipient of international awards: None

b) Member of a scholarly academy in a major country

AACR Member (American Association of Cancer Research)

c) Guest speaker or chair of related international conference and/or director or honorary member of a major international academic society in the subject field

Invited speaker at International Conference on Genome (ICG-8) 2013

Invited speaker at International Congress of Human Genetics 2016

d) Editor of an international academic journal: None

e) Peer reviewer for an overseas competitive research program (etc.): None

(2) Receipt of major large-scale competitive funds (over the past 5 years)

None

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

Variant analysis of SARS-CoV-2 genomes, 2020, Bull World Health Organ., 623

Emergence of Drift Variants That May Affect COVID-19 Vaccine Development and Antibody Treatment, 2020, Pathogens, 240

Enhancing Next-Generation Sequencing-Guided Cancer Care Through Cognitive Computing, Oncologist, 2017, 106

Comparing sequencing assays and human-machine analyses in actionable genomics for glioblastoma, 2017, Neurol Genet, 43

Watson for Genomics: Moving Personalized Medicine Forward, 2016, Trends in Cancer, 19

Evaluating Clinical Genome Sequence Analysis by Watson for Genomics, 2018, Frontiers in Medicine, 18
Evasion of vaccine-induced humoral immunity by emerging sub-variants of SARS-CoV-2, 2022, Future Microbiol, 14
Introductions and evolutions of SARS-CoV-2 strains in Japan, 2021, medRxiv, 11
Sequencing and curation strategies for identifying candidate glioblastoma treatments, 2019, BMC Medical Genomics, 9
Analysis on GENIE reveals novel recurrent variants that affect molecular diagnosis of sizable number of cancer patients, 2019, BMC Cancer, 7
Cross-Border Transmissions of the Delta Substrain AY.29 During Tokyo Olympic and Paralympic Games, 2022, Front Microbiol, 6

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

IBM Corporate Award for Watson for Genomics, May 2017 ($50,000 award)

Appendix 3-1 FY 2023 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Regarding the number of researchers at the Center, fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

We opened a WPI-Bio2Q account on LinkedIn (SNS) to proactively attract the attention of global scientists including research students. Various types of WPI-Bio2Q activities and job openings were posted, and specific messages were sent directly to scientists in related research fields. As a result, more than 800 scientists currently follow the WPI-Bio2Q account, and some of the followers are expected to apply for the WPI-Bio2Q Postdoc and Research Internship Program.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established overseas, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
N/A		

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
The Medical Research Council Laboratory of Molecular Biology (MRC-LMB)	Radu Aricescu	
Harvard Medical School	Jun Huh	
National University of Singapore	George Augustine	
The Central Institute for Experimental Animals (CIEA)	Erika Sasaki Makoto Suematsu	

2. Holding international research meetings

- Indicate the number of international research conferences or symposiums held in FY2023 and give up to three examples of the most representative ones using the table below.

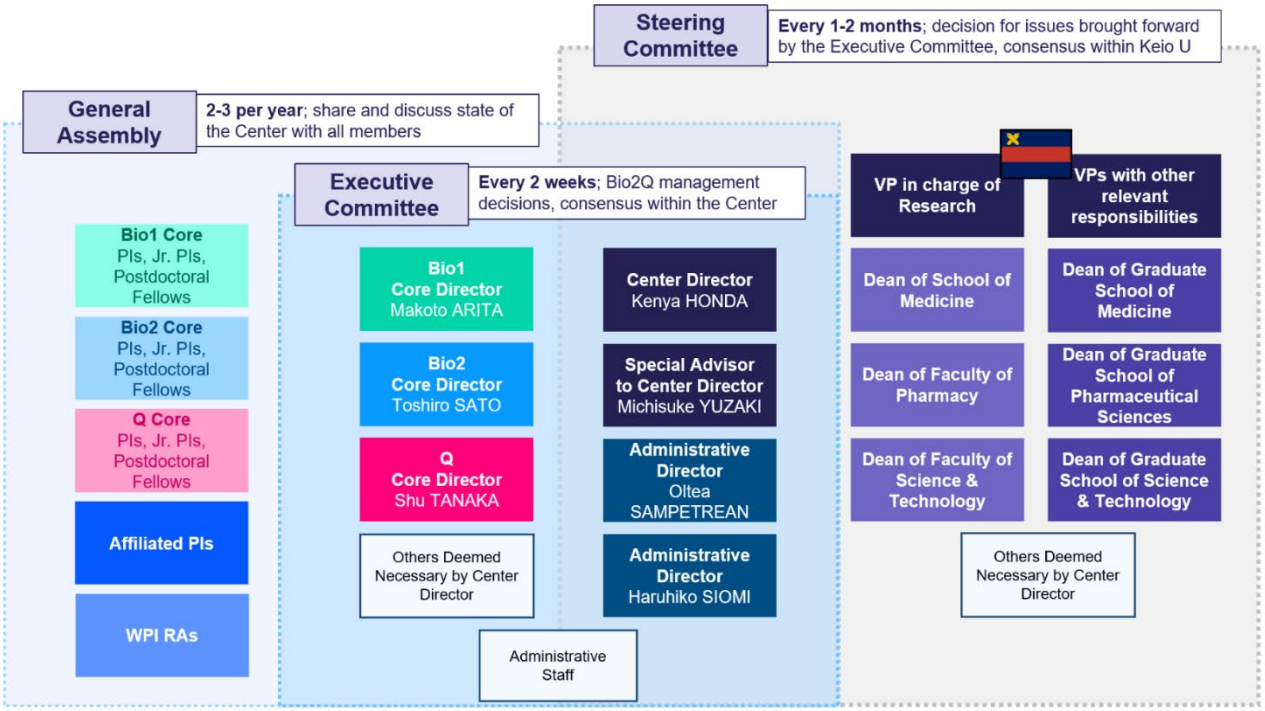
FY 2023: 2 meetings

Major examples (meeting titles and places held)	Number of participants
Keio University WPI-Bio2Q 2nd Symposium, Jul. 2023	From domestic institutions: 135 From overseas institutions: 51

CCEN-Bio2Q Meeting, the Cancer Convergence Education Network USA, Oct. 2023	From domestic institutions: 10 From overseas institutions: 22

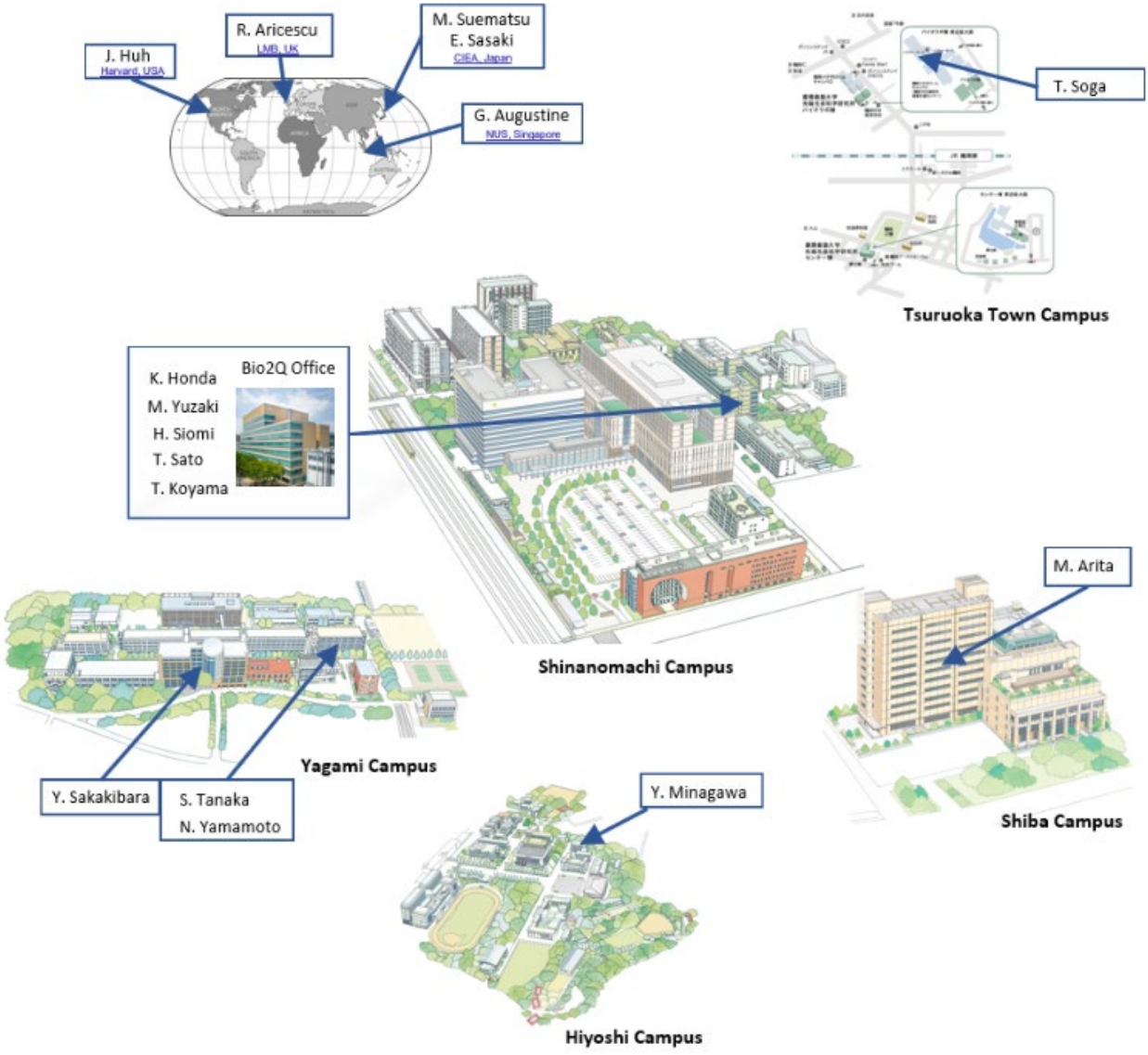
3. Diagram of management system

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).



4. Campus Map

- Draw a simple map of the campus showing where the main office and principal investigator(s) are located.



5. Securing external research funding*

External research funding secured in FY2023

Total: 1,618,733,023 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes "KAKENHI," funding for "commissioned research projects," "joint research projects," and for others (donations, etc.) as listed under "Research projects" in Appendix 3-2, Project Expenditures.

Organization	Fund name	Name	Period	Funding amount (Allowable amount)	Funding amount (FY2023)
AMED	Moonshot Research and Development Program	Kenya Honda Makoto Arita Michisuke Yuzaki Makoto Suematsu Erika Sasaki Koji Atarashi Timur Tuganbaev Oltea Sampetrean Yuki Sugiura Takako Hishiki Huizhuo Pan	2022-2027	Total 1,233,030,500 yen	203,305,700 yen
AMED	Project Focused on Developing Key Technology for Discovering and Manufacturing Drugs for Next-Generation Treatment and Diagnosis	Kenya Honda Koji Atarashi Oltea Sampetrean Timur Tuganbaev Kaoru Leong Huizhuo Pan	2021-2026	Total 1,212,771,400 yen	180,000,000 yen
JST	ERATO	Toshiro Sato Takako Hishiki	2023-2028	Total 1,678,860,000 yen	125,310,000 yen
KAKENHI	Specially Promoted Research	Kenya Honda	2020-2025	Total 650,000,000 yen	139,230,000 yen
JST	ERATO	Makoto Arita	2021-2026	Total 548,280,000 yen	44,930,000 yen
JST	Moonshot Research and Development Program	Toshiro Sato	2020-2025	Total 308,652,500 yen	92,804,400 yen
NEDO	Development of Quantum/ AI Hybrid Use-Case Technologies in Cyber-Physical Space	Shu Tanaka	2023-2024	Total 79,998,000 yen	39,999,000 yen

Appendix 3-1a FY 2023 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

* Fill in the number of researchers and other center staff in the table blow.
* Describe the final goals for achieving these numbers and dates when they will be achieved described in the last "center project."

a) Principal Investigators

（full professors, associate professors or other researchers of comparable standing)

(number of persons)

	At the beginning of project	At the end of FY 2023	Final goal (Date: March, 2025)
Researchers from within the host institution	10	11	11
Researchers invited from overseas	3	3	3
Researchers invited from other Japanese institutions	2	2	2
Total principal investigators	15	16	16

b) Total members

	At the beginning of project		At the end of FY 2023		Final goal (Date: March, 2025)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	33		41		90	
Overseas researchers	13	39	18	44	28	31
Female researchers	8	24	11	27	45	50
Principal investigators	15		16		16	
Overseas PIs	3	20	3	19	3	19
Female PIs	2	13	2	13	2	13
Other researchers	18		23		62	
Overseas researchers	10	56	13	57	19	31
Female researchers	6	33	7	30	36	58
Postdocs	0		2		12	
Overseas postdocs	0	0	2	100	6	50
Female postdocs	0	0	2	100	7	58
Research support staffs	1		5		15	
Administrative staffs	6		13		11	
Total number of people who form the "core" of the research center	40		59		116	

	At the beginning of project		At the end of FY 2023		Final goal (Date: March, 2025)	
	Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students	0		0		40	
Employed	0	-	0	-	40	100.0

※b) The number of doctoral students in the lower table can be duplicated in the upper table of overall composition.

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the "Total costs" column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the "Amount covered by WPI funding" column, enter the amount covered by WPI within the total amount.
* In the "Personnel," "Project activities," "Travel," and "Equipment" blocks, the items of the "Details" column may be changed to coincide with the project's actual content.

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):16	133	8
	Other researchers (no. of persons):25	80	31
	Research support staff (no. of persons):5	14	14
	Administrative staff (no. of persons):13	43	43
	Subtotal	270	96
Project activities	Gratuities and honoraria (no. of persons):11	2	2
	Cost of Bio2Q branding design	4	4
	Cost of Website	1	1
	Cost of outreach activity	6	6
	Research startup cost (no. of persons):2	1	1
	Cost of international symposiums (no. of symposiums):1	3	3
	Cost of consumables	25	22
	Rental fees for facilities	54	0
	Cost of utilities	7	0
	Other costs	9	4
	Subtotal	112	43
Travel	Domestic travel costs	0	0
	Overseas travel costs	1	1
	Travel and accommodations cost for invited scientists (no. of domestic scientists):3 (no. of overseas scientists):8	3	3
	Travel cost for scientists on transfer (no. of domestic scientists):0 (no. of overseas scientists):1	1	1
	Subtotal	5	5
Equipment	Facility renovation and improvement	159	159
	Costs of research equipments and office equipments	574	557
	Subtotal	733	716
Research projects (Detail items must be fixed)	KAKENHI	390	
	Commissioned research projects, etc.	1,115	
	Joint research projects	33	
	Ohers (donations, etc.)	80	
	Subtotal	1,618	0
Total (*Includes carryover of WPI grant in FY 2022.)		2,738	860

Costs (Million yens)

WPI grant in FY 2023	716
Costs of establishing and maintaining facilities	159
Repairing facilities	159
(Number of facilities:4, 1084.6m²)	
Others	0
Costs of equipment procured	557
Freezers(Number of units:5)	6
Microscopes(Number of units:5)	95
Safety cabinets(Number of units:3)	8
Others	448

*Of the 650 million yen in WPI Grant in FY2022, 560 million yen was carried over to FY2023.

*Of the 700 million yen in WPI Grant in FY2023, 400 million is carried over to FY2024.

*1. Management Expenses Grants (including Management Enhancements Promotion Expenses (機能強化経費)), subsidies including National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc., indirect funding, and allocations from the university's own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by KAKENHI or under commissioned research projects or joint research projects, the amounts should be entered in the "Research projects" block.

*1 運営費交付金（機能強化経費を含む）、国立大学改革強化推進補助金等の補助金、間接経費、その他大学独自の取組による学内リソースの配分等による財源
*2 科研費、受託研究費、共同研究費等によって人件費、旅費、設備備品等費を支出している場合も、その額は「研究プロジェクト費」として計上すること

Appendix 4 FY 2023 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2023 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2024 and not described in Appendix 1.

Overseas Satellite 1 **Name** (Total: OO papers)

1) N/A
2)
3)
4)

Overseas Satellite 2 **Name** (Total: OO papers)

1) N/A
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2023. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1: N/A

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2023					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2023					

Overseas Satellite 2: N/A

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2023					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2023					

Appendix 5　FY 2023 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.
* Enter the host institution name and the center name in the footer.

Total: 9

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Jose C. Clemente, Ph.D.	50	Associate Professor Department of Genetics and Genomic Sciences Department of Medicine Icahn Institute for Genomics & Multiscale Biology Precision Immunology Institute Icahn School of Medicine at Mount Sinai	USA	Ph.D. Genomic Sciences Precision Immunology	PRINCIPAL INVESTIGATOR | Google Scholar Jose is a computational biologist. He is an Assistant Professor in the Department of Genetics and Genomic Sciences and the Immunology Institute at the Icahn School of Medicine at Mount Sinai. He received is B.Sc. from University of Seville (Spain), and his M.Sc. and Ph.D. from the Japan Advanced Institute of Science and Technology (Japan). He did his postdoctoral training at the National Institute of Genetics (Japan) and at the University of Colorado. His lab develops computational and experimental methods to understand the microbiome and its relation to immune and metabolic disorders. He is a rabid Emacs user.	2023 July 12 - 14 3 days	1)Attended the WPI-Bio2Q Open Seminar as a speaker. WPI-Bio2Q Open Seminar Gut Microbiome Seminar July 13, 2023
2	Sloan Devlin, Ph.D.	39	1) Associate Professor Department of Biological Chemistry and Molecular Pharmacology Harvard Medical School 2)International Collaborator WPI-Bio2Q	USA	Ph.D. Biological Chemistry and Molecular Pharmacology	Sloan's current work focuses on leveraging expertise in organic chemistry, analytical chemistry, biochemistry, microbiology, cell biology, and gnotobiotic in vivo experiments to understand how human gut bacteria contribute to health and disease. The Journal of Clinical Investigation Lectureship Award, 2023 ASBMB Deuel Lipids Conference Alfred P. Sloan Research Fellowship, chemistry, 2021 NIH Maximizing Investigators' Research Award (MIRA) (R35), 2018 John and Virginia Kaneb Junior Faculty Fellowship, 2018 Karin Grunebaum Cancer Research Foundation Fellow, 2017-2018 Roger Davis Investigator Award, Kern Lipid Conference, 2017	2023 July 21 - 31 11 days	1)Attended the WPI-Bio2Q Open Seminar as a speaker. WPI-Bio2Q Open Seminar Gut Microbiome Seminar Monday, July 24, 2023 2)Attended the WPI-Bio2Q 2nd Symposium as a speaker. July 27, 2023
3	Jun Huh, Ph.D.	50	1)Principal Investigator Associate Professor of Immunology, Harvard Medical School 2)Principal Investigator WPI-Bio2Q	USA	Ph.D. Immunology	Jun was selected as a recipient of the Jane Coffin Childs Memorial Fund Postdoctoral Fellowship (2006), the NIH Pathway to Independence (PI) Award (2011), and the Smith Family Awards Program for Excellence in Biomedical Research (2013). He has been named a 2015 Searle Scholar and 2016 Pew Scholar.	2023 July 26 - August 2 8 days	1)Attended the WPI-Bio2Q 2nd Symposium as a speaker. July 27, 2023 2)Attended the WPI-Bio2Q Open Seminar as a speaker. July 28, 2023

4	Kunimichi Suzuki, Ph.D.	38	1) Investigator Scientist Neurobiology Department Laboratory of Molecular Biology Medical Research Council, UK 2)Junior Principal Investigator WPI-Bio2Q	UK	Ph.D. Neurobiology	Jul, 2022 - Present: Investigator Scientist, Neurobiology, MRC Laboratory of Molecular Biology Sep, 2019 - Present: School of Medicine, Keio University Sep, 2019 - Jul, 2022: Visiting scientist, Neurobiology division, MRC Laboratory of molecular biology Apr, 2013 - Aug, 2019: School of Medicine, Keio University Mar, 2021: Seal of Excellence, European Commission Horizon 2020	2023 July 26 - August 16 22 days	1)Attended the WPI-Bio2Q 2nd Symposium as a speaker. July 27, 2023
5	Gloria Choi, Ph.D.	46	1)Associate Professor, the Department of Brain and Cognitive Sciences and Investigator in the Picower Institute for Learning and Memory / MIT 2)International Collaborator WPI-Bio2Q	USA	Ph.D. Brain and Cognitive Sciences	Choi's lab studies the interaction of the immune system with the brain and the effects of that interaction on neurodevelopment, behavior and mood. For example, she is particularly interested in learning how cytokines, families of proteins that immune cells use to communicate, may act as neuromodulators that influence the development and activity of neurons in the cortex. In a 2016 paper in Science, Choi and collaborators showed in a mouse model of maternal immune activation that a particular type of T lymphocyte immune cell and its secretion of the cytokine interleukin-17a (IL-17a), mediated maternal immune activation and the development of autism-like behavioral abnormalities in offspring. The collaboration then followed with two papers in Nature in September 2017. One showed the phenomenon was further mediated by the presence of maternal intestinal bacteria that promote T cell differentiation. The other showed that the effect of IL-17a in the brain was focused in the S1DZ region of the cortex where they observed a deficit of neural inhibition. The team showed that by intervening to reduce excess neural activity, they could mitigate behavioral abnormalities associated with maternal infection. 2014 Cell's 40 under 40 2017 NARSAD Independent Investigator Award 2018 The Peter Gruss Young Investigator Award 2019 Nancy Lurie Marks Family Foundation (NLMFF) Career	2023 July 26 - August 2 8 days	1)Attended the WPI-Bio2Q 2nd Symposium as a speaker. July 27, 2023 2)Attended the WPI-Bio2Q Open Seminar July 28, 2023

6	Arnold J. Levine, Ph.D.	85	Institute for Advanced Study	USA	Ph.D. Molecular Biology	Levine discovered, with several colleagues, the p53 tumor suppressor gene in 1979, a protein involved in cell cycle regulation, and one of the most frequently mutated genes in human cancer, in work done as a professor in the biochemistry department at Princeton University. In 1979 Levine moved to become chairman of the department of microbiology at Stony Brook School of Medicine before moving back to Princeton in 1984. In 2002 he was appointed professor at The Cancer Institute of New Jersey in New Brunswick, New Jersey, then a part of the Robert Wood Johnson Medical School. Simultaneous to this appointment, in 2003, Levine became a visiting professor, then professor, in the newly created Simons Center for Systems Biology at the Institute for Advanced Study (IAS) in Princeton, New Jersey, where he has remained since. Award and honors Louisa Gross Horwitz Prize (Columbia University) (1998) Albany Medical Center Prize (2001), Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research (1994), Charles S. Mott Prize from the General Motors Cancer Research Foundation (1999), Keio Medical Science Prize (2000) Memorial Sloan-Kettering Cancer Center's Medal for Outstanding Contributions to Biomedical Research (2000), Albany Medical Center Prize in Medicine and Biomedical Research (2001)	2023 October 10 1 day	1)Attended the CCEN-Bio2Q meeting as a speaker. October 10, 2023 CCEN: Cancer Convergence Education Network Other speakers: Columbia University, USA Stanford University, USA New York University Langone Center, USA Northwestern University, USA MD Anderson Cancer Center, University of Texas, USA Hans Clevers Laboratory, Hubrecht Institute, The Netherlands Memorial Sloan Kettering Cancer Center, USA Keio University School of Medicine, Japan
7	George Augustine, Ph.D.	68	1)Temasek Senior Investigator, Temasek Life Sciences Laboratory, National University of Singapore 2)Principal Investigator WPI-Bio2Q	Singapore	Ph.D. Neurobiology	Prof Augustine is well-known for his studies of brain synaptic mechanisms. His laboratory has shown that neurotransmitter release is triggered by a remarkably local calcium signal; have identified the roles of many proteins involved in neurotransmitter release; and have identified the role of calcium ions and other chemical signals in transducing brief neuronal activity into long-lasting change in brain function. His group also has developed novel optogenetic technologies and is applying these to study brain circuit function. He has published more than 200 articles and has served on the editorial boards of numerous scientific journals, including Neuron, the Journal of Neuroscience, the Journal of Physiology, Frontiers in Neural Circuits, Neurophotonics and Cells, as well as serving as the founding editor of Brain Cell Biology. He also is well-known as a co-author of the internationally popular Neuroscience textbook (Oxford University Press).	2023 December 5 - 15 11 days	1)Attended the WPI-Bio2Q Presentation skills Lecture & workshops as a lecturer December 5 - 15, 2023

8	Ken Cadwell, Ph.D.		Professor, Penn Institute for Immunology Perelman School of Medicine University of Pennsylvania	USA	Ph.D. Immunology	"My laboratory investigates how our immune system has adapted to the diverse microbial agents we encounter in our lifetime. We address this question by focusing on the gastrointestinal tract where a single layer epithelium separates our body from pathogens and microbial colonizers belonging to the microbiota. Through taking a comparative infection biology approach, our research has identified cellular mechanisms underlying the balanced immune response that is necessary for responding to life-threatening infections while avoiding chronic illnesses like inflammatory bowel disease. Ongoing projects include elucidating how symbiotic intestinal viruses, fungi, and parasites contribute to local and extraintestinal disease susceptibility, defining how the cellular pathway of autophagy mediates resilience towards infectious threats, and understanding how polymicrobial exposure in the natural environment contributes to the developmental maturation of the immune system. Through these projects, we hope to gain further insight into how microbial diversity in the intestinal ecosystem shapes host physiology and pave the way for therapies that restore balanced host-microbe relationships."	2024 January 19 1 day	1)Attended the WPI-Bio2Q Open Seminar as a speaker. January 19, 2024
9	Eleni Kotsiliti, Ph.D.		Senior Editor Nature Reviews Gastroenterology & Hepatology Springer Nature	Germany	Ph.D. Immunology	Eleni studied for a BSc and a MSc in Biology and Molecular biology, respectively, at the University of Patras. Next, she carried out her PhD studying the immunology of nonalcoholic steatohepatitis (NASH) at the Technical University of Munich, Helmholtz Center, under the supervision of Prof. Dr Mathias Heikenwälder. She continued with her NASH research as a postdoc at the German Cancer Center in Heidelberg in the Heikenwälder lab. In August 2021, Elena joined Nature Reviews Gastroenterology & Hepatology as an Associate Editor. She was promoted to Senior Editor in September 2023.	2024 March 25 1 day	1)Attended the WPI-Bio2Q Open Seminar as a speaker. March 25, 2024

Appendix 6 FY2023 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2023 by each activity.
* Describe the outreach activities in the "3-1. Societal Value of Basic Research" of Progress Report, including those stated below that warrant special mention.

Activities	FY2023 (number of activities, times held)
PR brochure, pamphlet	5 -Bio2Q Donor Leaflet, Jun. 2023 -Bio2Q Center Introduction, Nov. 2023 (https://bio2q.keio.ac.jp/#digital-downloads) -Bio2Q Kenya Honda, Nov. 2023 (https://bio2q.keio.ac.jp/#digital-downloads) -Bio2Q Michisuke Yuzaki, Mar. 2024 (https://bio2q.keio.ac.jp/#digital-downloads) -Bio2Q Haruhiko Siomi, Mar. 2024 (https://bio2q.keio.ac.jp/#digital-downloads)
Lectures, open scientific seminars and events for the general public	10 -Bio2Q Open Seminar Jose C. Clemente, Icahn School of Medicine at Mount Sinai, USA, Jul. 2023 (https://bio2q.keio.ac.jp/news/keio-university-wpi-bio2q-gut-microbiome-seminar/) -Bio2Q Open Seminar Sloan Devlin, Harvard Medical School, USA, Jul. 2023 (https://bio2q.keio.ac.jp/news/keio-university-wpi-bio2q-gut-microbiome-seminar-2/) -Bio2Q Open Seminar, Jun Huh, Harvard Medical School, USA, Jul. 2023 (https://bio2q.keio.ac.jp/news/keio-university-wpi-bio2q-open-seminar/) -Keio University WPI-Bio2Q 2nd Symposium, Jul. 2023 (https://bio2q.keio.ac.jp/news/keio-university-wpi-bio2q-2nd-symposium/) -Bio2Q Open Seminar, the Cancer Convergence Education Network, USA, Oct. 2023 (https://bio2q.keio.ac.jp/news/ccen-bio2q-meeting/) -Bio2Q Open Seminar, A presentation skills lecture, by WPI-Bio2Q PI Prof. George J. Augustine, Dec. 2023 (https://bio2q.keio.ac.jp/news/presentation-skills-lecture-for-keio-university-faculty-students-and-staff/) -Bio2Q Open Seminar, Ken Cadwell, Ph.D., Professor, Penn Institute for Immunology, Perelman School of Medicine, University of Pennsylvania, USA, Jan. 2024 (https://bio2q.keio.ac.jp/news/wpi-bio2q-open-seminar-keio-university-members-only/) -S&TDC -WPI Online Seminar, Feb. 2024 -Bio2Q Open Seminar Takanori Kanai, Ph.D., Professor, Keio University School of Medicine, Feb. 2024 (https://bio2q.keio.ac.jp/news/wpi-bio2q-open-seminar-for-keio-university-members-to-be-hold/) -Bio2Q Open Seminar, Elini Kotsiliti, Ph.D., Senior Editor, Nature Review Gastroenterology & Hepatology, Springer Nature, Germany, Mar. 2024 (https://bio2q.keio.ac.jp/news/wpi-bio2q-open-seminar-for-keio-university-members-to-be-held-on-march-25/)
Internal HR Seminars	11 - Jr. PI Candidate, Apr. 2023 (1) - PI Candidate and Postdoctoral Fellow Candidate, Jul. 2023 (2) - Jr. PI Candidates, Aug. 2023 (2) - Postdoctoral Fellow Candidate, Sep. 2023 (1) - Jr. PI Candidates, Nov. 2023 (2) - Postdoctoral Fellow Candidates, Jan. 2024 (2) - PI Candidate, Mar. 2024 (1)
Teaching, experiments, training for elementary, secondary and high school students	2 -12th WPI Science Symposium at ICReDD, Dec. 2023

	(https://bio2q.keio.ac.jp/news/12th-wpi-science-symposium-for-junior-high-and-high-school-students-and-the-general-public/) -JST Global Science Campus, Dec. 2023 (https://www.jst.go.jp/cpse/gsc/)
Science Meeting	1 (9 times) -Bio2Q Science Meeting Series (9 times) (Internal scientific discussion)
Tea Time, Lunch Time	1 (7 times) -Bio2Q Tea Time, Lunch Time (7 times) (Internal social event)
Participating, exhibiting in events	2 -Bio Japan 2023, Dec. 2023 (https://bio2q.keio.ac.jp/news/bio-japan-2023/) -Metabolome Symposium 2023, Dec. 2023 (https://bio2q.keio.ac.jp/news/metabolome-symposium-2023/)
Press / News releases	5 -Keio University Press release, Aug. 2023 Title: Keio University WPI-Bio2Q 2nd Symposium (https://www.keio.ac.jp/en/news/2023/Aug/8/48-142695/) -Professor Michisuke Yuzaki to receive a national Medal of Honor, the Medal with Purple Ribbon, Nov. 2023 (https://bio2q.keio.ac.jp/news/professor-michisuke-yuzaki-is-being-awarded-a-national-medal-of-honor-the-medal-with-purple-ribbon-in-november-2023/) -Bio2Q Anniversary Event, Dec. 2023 (https://bio2q.keio.ac.jp/news/wpi-bio2q-anniversary-event-held-on-thursday-december-14-2023/) -Dr. Therese Solberg awarded Dr. Lutz und Dr. Celia Zwillenberg Prize by the University of Bern, Dec.2023 (https://bio2q.keio.ac.jp/news/dr-therese-solberg-awarded-dr-lutz-und-dr-celia-zwillenberg-prize-by-the-university-of-bern/) -3 of our faculty members were included in Clarivate's 2023 Highly Cited Researchers list. Dec. 2023 (https://bio2q.keio.ac.jp/news/3-wpi-bio2q-faculty-members-named-most-highly-cited-in-the-world/)
Publications of the popular newspapers	1 -The Japan times, May 2023 Sustainability a key focal point of education and research (https://www.japantimes.co.jp/2023/05/19/special-supplements/hiroshima-g7-summit-special/sustainability-key-focal-point-education-research/)
SNS	2 -Launched Bio2Q account page on LinkedIn, Jun. 2023 (Five posts per month) -Launched Bio2Q account page on X., Jun. 2023 (Three posts per month)
Promotional video	1 -WPI promotional video (Bio2Q), Mar. 2023 (https://www.youtube.com/watch?v=A55A5UvitOs&list=PLDQHaku44paEtbtqy4wwtlkWojm1P3rcO&index=17)

*If there are any rows on activities the center didn't implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after "Others" on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of "Others" can be added, if needed.

Outreach Activities and Their Results

List up to three of the Center's outreach activities carried out in FY 2023 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, and describe its concrete contents and effect in narrative style. (Where possible, indicate the results in concrete numbers.)

Examples:

- As a result of using a new OO press-release method, a OO% increase in media coverage was obtained over the previous year.
- By holding seminars for the public that include people from industry, requests for joint research were received from companies.
- We changed our public relations media. As a resulting of using OO to disseminate information, a OO% increase in inquiries from researchers was obtained over the previous year.
- As a result of vigorously carrying out OO outreach activity, \OO in external funding was acquired.

1) Keio University WPI-Bio2Q 2nd Symposium was held onsite/online at Keio University Shinanomachi Campus in Tokyo on July 27, 2023, with sessions by ten of the world's top scientists from Harvard University (USA), MIT (USA), MRC Laboratory of Molecular Biology (UK), and Keio University. The sessions included introductions to each scientist's area of expertise as well as time for questions and answers. As a result, a total of 186 scientists, including 135 from Japan, 19 from USA, 5 from India, 3 from Italy, 2 from Singapore, and 22 from other countries, or 119 males and 67 females, participated onsite/online, and the global participants engaged in lively discussions on how to achieve good health and longevity in society through the integration of human biology, the microbiome, and quantum computing, as well as the future development of new life sciences.

2) Bio2Q launched its account page on LinkedIn to introduce its activities to the world's scientists. News was posted five times a month. As a result, currently more than 800 scientists from USA, EU and Asia are successfully following the Bio2Q page. Bio2Q now maintains communication with these followers to discuss many valuable sciences, and some scientists have applied for jobs at Bio2Q.

3) Bio2Q held a science session for 40 top high school students from all over Japan at the JST Global Science Campus. Bio2Q's Professor Siomi's talk about Epigenome was very interesting for the students. As a result, further discussions were followed with 8 students who showed great interest in WPI and Bio2Q activities.

Appendix 7 FY 2023 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2023.

* Enter the host institution name and the center name in the footer.

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	May 19, 2023	newspaper	-The Japan times May 19, 2023 Sustainability a key focal point of education and research (https://www.japantimes.co.jp/2023/05/19/special-supplements/hiroshima-g7-summit-special/sustainability-key-focal-point-education-research/)
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